JOC The Journal of Organic Chemistry

Article

Stereoselective Synthesis of Highly Substituted Tetrahydropyrans through an Evans Aldol-Prins Strategy

Sergio J. Álvarez-Méndez, Marta Fariña-Ramos, María Luisa Villalba, Marcelle D. Perretti, Celina Garcia, Laila Moujir Moujir, Miguel A. Ramírez, and Victor S. Martin

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b01182 • Publication Date (Web): 23 Jul 2018

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Stereoselective Synthesis of Highly Substituted Tetrahydropyrans through an Evans Aldol-Prins Strategy

Sergio J. Álvarez-Méndez [†*], *Marta Fariña-Ramos*[†], *María Luisa Villalba*[‡], *Marcelle D. Perretti*[†], *Celina García*[†], *Laila M. Moujir*[§], *Miguel A. Ramírez*[†], *and Víctor S. Martín*[†*]

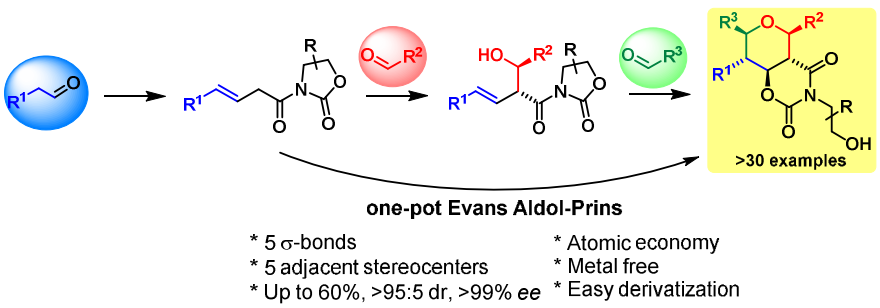
[†] Instituto Universitario de Bio-Orgánica "Antonio González" (IUBO-AG), Centro de Investigaciones Biomédicas de Canarias (CIBICAN), Departamento de Química Orgánica, Universidad de La Laguna (ULL), Avda. Astrofísico Francisco Sánchez 2, 38206 San Cristóbal de La Laguna (Tenerife), Spain.

[‡] Laboratorio de Investigación y Desarrollo de Bioactivos (LIDeB), Departamento de Ciencias Biológicas, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, Argentina, 47 & 115, B1900AJI La Plata, Buenos Aires, Argentina.

[§] Departamento de Bioquímica, Microbiología, Biología Celular y Genética, Facultad de Farmacia, Universidad de La Laguna (ULL), Avda. Astrofísico Francisco Sánchez s/n, 38206 San Cristóbal de La Laguna (Tenerife), Spain.

* *E-mails: salvmen@ull.edu.es, vmartin@ull.edu.es*

ABSTRACT GRAPHIC



[*] Sergio J. Álvarez-Méndez's current address: Sección de Ingeniería Agraria, Escuela Politécnica Superior de Ingeniería, Universidad de La Laguna (ULL), Carretera San Miguel de Geneto 2, 38296 San Cristóbal de La Laguna (Tenerife), Spain.

ABSTRACT

A direct and general method for the synthesis of naturally occurring 2,3,4,5,6-pentasubstituted tetrahydropyrans has been developed, employing β,γ-unsaturated *N*-acyl oxazolidin-2-ones as key starting materials. The combination of the Evans aldol addition and the Prins cyclization allowed the diastereoselective and efficient generation of the desired oxacycles in two fashions: a one-pot Evans aldol-Prins protocol, in which five new σ bonds and five contiguous stereocenters were straightforwardly generated, and a two-steps version, which additionally permitted the isolation of precursors β,γ-unsaturated alcohols bearing an *N*-acyl oxazolidin-2-one in the α position. From these alcohols were also obtained halogenated pentasubstituted tetrahydropyrans as well as 2,3,4,5-tetrasubstituted tetrahydrofurans, shedding light on the mechanism of the process. Computational studies were consistent with the experimental findings, and this innovative Evans aldol-Prins strategy conducted to the preparation of a battery of more than 30 densely substituted tetrahydropyrans, unprecedentedly fused to a 1,3-oxazinane-2,4-dione ring, both in a racemic and in a enantiomeric fashion. These novel molecules were successfully submitted to several transformations to permit a simple access to a variety of differently functionalized tetrahydropyrans. Most of these unique molecules were evaluated for their antimicrobial activity against Gram-positive and Gram-negative bacteria and the yeast *Candida albicans* and some structure/activity relationships were established.

INTRODUCTION

The tetrahydropyran (THP) motif is commonly found in biologically active secondary metabolites isolated from marine and terrestrial sources, such as those shown in Figure 1, as well as being part of complex cyclic polyether systems.[1] For example, 2,3,5-

trisubstituted THPs can be found in morinols A and B, isolated in 1999 from *Morina chinensis*, a plant employed in the traditional Chinese medicine.[2] Morinols and some derivatives show antiproliferative,[3] antimicrobial[4] and antifungal activity.[5] Higher substituted THPs can be found in clavosolides A and B, which exhibit two 2,3,4,6-tetrasubstituted THPs in their structures. They were isolated from the cytotoxic extract of the sponge *Myriastra clavosa* from the Philippines.[6] The same substitution and stereochemical pattern appears in the tetrasubstituted THP bore by the family of toxins polycavernosides, isolated from the red alga *Gracilaria edulis* (also known as *Polycavernosa tsudai*).[7] Kendomycin, which was isolated from several *Streptomyces* strains, shows a 2,3,4,5,6-pentasubstituted THP with the substituent at C_5 adopting an axial disposition. This compound acts as an endothelin receptor antagonist and it also exhibits cytotoxicity against multiple human cell line and antiosteoporotic and antibiotic activities.[8] Phorboxazoles A and B were isolated from Indian Ocean sponge *Phorbas* sp. and show antitumor activity and antifungal activity against *Candida albicans*.[9] Four THPs rings appear in their structures, underlining the presence of the THP labelled as B (Figure 1) with substituents in all its positions and the same substitution pattern found in kendomycin. Besides being part of bioactive natural products, it has been demonstrated that the THP ring can even improve the efficacy of antiviral drugs,[10] and it can show bioactivity itself, such as antinociceptive activity,[11] serotonin and norepinephrine transporter inhibitory activity,[12] antimicrobial activity by the inhibition of bacterial topoisomerase[13] and antiproliferative activity.[14]

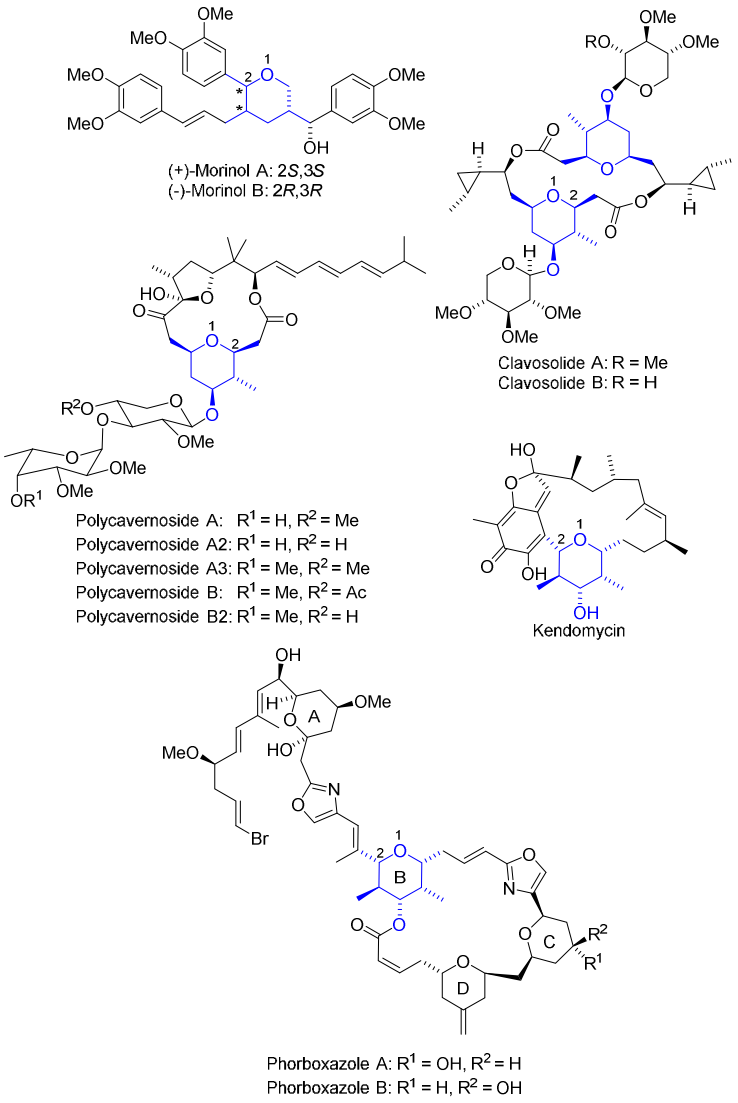


Figure 1. Examples of natural products containing non-fused densely substituted THPs.

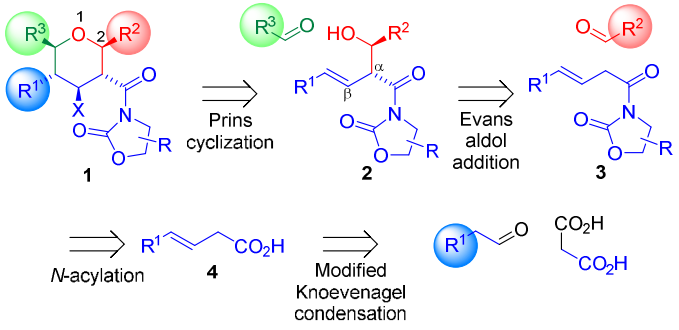
The number of natural products containing a THP ring has encouraged the development and application of many synthetic strategies to achieve its obtaining, such as Pd-catalyzed oxaheterocyclization,[15] Petasis-Ferrier union/rearrangement tactic,[16] Michael-like reactions,[17] S_N-mediated and metal-promoted cyclizations,[17] ester enolate Claisen rearrangement,[18] ring expansion of tetrahydrofurans,[18] 1,5-cyclization,[18] iodolactonization,[18] epoxide opening-ring closure reactions,[18] and so on.[19] Among the existing tactics, the Prins cyclization[20] has emerged for the last years as a handy tool that affords the access to desired THPs.[21] Throughout the last decade, our research

group, has taken advantage of the Prins cyclization to synthesize differently substituted six- and seven-membered oxa- and aza-heterocycles.[22] Nevertheless, the application of the Prins cyclization to access challenging 2,3,4,5,6-pentasubstituted THPs has not been systematically studied. On the one hand, there are only a few examples as part of methodological works oriented to the obtaining of THPs with a less populated substitution design.[22e,23-26] On the other hand, Rychnovsky and co-workers have employed Prins cyclization to build pentasubstituted THPs to synthesize some natural products.[27-29]

This absence of a general method encouraged us to propose a strategy based in the combination of the well-known Evans aldol addition, as a powerful tool to construct the necessary homoallylic alcohol, and the Prins cyclization to yield the target highly substituted THPs (Scheme 1).[30] Thus, this Evans aldol-Prins (EAP) protocol suggests that a 2,3,4,5,6-pentasubstituted THP **1** could be accessed via the Prins cyclization of an aldehyde R^3CHO and the *syn*-aldol **2**.[31] β,γ-Unsaturated alcohols **2** bear a *N*-acyl oxazolidin-2-one moiety at α position. This auxiliary is the key for introduction of the stereochemistry in the aldol and, therefore, in the subsequent THP **1**. Evans aldol addition was proposed as the diastereoselective pathway to get the aldol **2** starting from a generic aldehyde R^2CHO and β,γ-unsaturated *N*-acyl oxazolidin-2-one **3**.[32] Compounds **3** may be prepared from the appropriate oxazolidin-2-one via an *N*-acylation of β,γ-unsaturated carboxylic acids **4**.[33] Several of these acids are commercially available, though they also can be readily synthesized via a modified Knoevenagel condensation starting from aldehydes R^1CH_2CHO.[34] Thus, the envisioned tactic should allow the stereoselective access to an enormous structural complexity by the consecutive combining of three different aldehydes in four reaction steps. Prior to establish an asymmetric strategy, non-chiral oxazolidin-2-one were firstly selected as

Evans auxiliary to evaluate its influence in this unprecedented process. In this report, we expand the results previously published[30] in order to exhaustively detail all the studies that led us to establish a protocol to yield 2,3,4,5,6-pentasubstituted THPs in a general and diastereoselective fashion. A special emphasis has been giving herein to the different reaction conditions screenings and to the identification of all the by-products and minor stereoisomers associated to the EAP protocol. We have also delved into mechanistic studies, the enantiomeric approach and the derivatization and biological evaluation of the novel family of compounds synthesized.

Scheme 1. Retrosynthetic Analysis to Access 2,3,4,5,6-Pentasubstituted THPs via an Evans Aldol-Prins Strategy

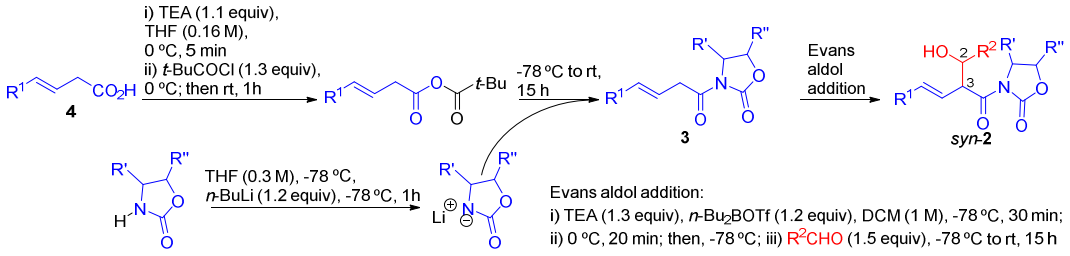


RESULTS AND DISCUSSION

As shown in Scheme 1, our synthetic approach firstly requires the preparation of a set of *N*-acyl oxazolidin-2-ones **3** employing carboxylic acids **4** as starting materials (Table 1). Acids **4a-4c** were commercially available, whereas acids **4d-4f** were straightforwardly obtained via a solvent-free condensation/decarboxylation sequence.[34] Acids **4** were differently activated prior to their subsequent treatment with the lithiated oxazolidin-2-one to yield **3**. Both systems DMF/oxalyl chloride[35] and DCC/DMAP[36] proved to be efficient, albeit we eventually selected TEA/pivaloyl chloride[33] as reagents due to the compatibility with the multigram synthesis of **3a** (Table 1, entry 1). With these

conditions in hand, non-chiral *N*-acyl oxazolidin-2-ones **3b-3f** (entries 2-6) and chiral *N*-acyl oxazolidin-2-ones **3g-3i** (entries 7-9) were efficiently synthesized with yields ranging from 60 to 90%, except when the starting acid bore a terminal double bond (**4b**, R^1 = H), since undesired *E*-α,β-**3b** was also obtained as consequence of the isomerization of the double bond (entry 2).[37] *N*-Acyl oxazolidin-2-ones **3a-3c** were submitted to the Evans protocol to gain access to various *syn*-aldols **2** with good yields and showing an excellent tolerance to aromatic groups and both linear and branched aliphatic chains (entries 10-17).[32] Similarly, chiral aldols **2i-2m** were obtained from *N*-acyl oxazolidin-2-ones **3g-3i** (entries 18-22). As expected, in all the cases *syn*-aldols were exclusively obtained except when a non-properly stored *n*-Bu_2BOTf solution was employed (entry 10), due to the diastereoselectivity of the aldol addition may be sensitive to the concentration of that reagent.[38] Isolation of traces of *anti*-**2a** invited us to try the efficient and selective access to that aldol, although the employment of the methods previously published by Evans[39] and Hoye[40] were unsuccessful. Additionally, when *N*-acyl oxazolidin-2-one **3c**, bearing a double bond with a *Z* geometry, was selected as starting material, it was observed a partial isomerization of the double bond in the final product, leading to desired **2g** with a moderate yield (entry 16).

Table 1. Synthesis of the *N*-Acyl Oxazolidin-2-ones 3 and Aldols 2



N-acylation						Evans aldol addition			
Entry	**Acid**	R^1	R'	R''	**3** (%)	Entry	**3**	R^2	**2** (%)[c]

1	**4a**	Et	H	H	**3a** (68)[a]	10	**3a**	*i*-Bu	**2a** (81)[d]
2	**4b**	H	H	H	**3b** (39)[b]	11	**3a**	Me	**2b** (75)
3	**4c**	(*Z*)-Me	H	H	**3c** (75)	12	**3a**	Bu	**2c** (84)
4	**4d**	$PhCH_2$	H	H	**3d** (60)	13	**3a**	Ph	**2d** (81)
5	**4e**	*n*-pentyl	H	H	**3e** (90)	14	**3a**	$PhCH_2CH_2$	**2e** (81)
6	**4f**	$BnOCH_2CH_2$	H	H	**3f** (60)	15	**3b**	Me	**2f** (76)
7	**4a**	Et	(*R*)-Bn	H	**3g** (90)	16	**3c**	*i*-Bu	**2g** (48)[e]
8	**4a**	Et	(*S*)-*i*-Pr	H	**3h** (83)	17	**3a**	4-Br-Ph	**2h** (59)
9	**4a**	Et	(*R*)-Me	(*S*)-Ph	**3i** (87)	18	**3g**	Me	**2i** (75)[f]
						19	**3g**	$PhCH_2CH_2$	**2j** (60)[f]
						20	**3h**	Me	**2k** (86)[g]
						21	**3h**	$PhCH_2CH_2$	**2l** (69)[g]
						22	**3i**	Bu	**2m** (64)[f]

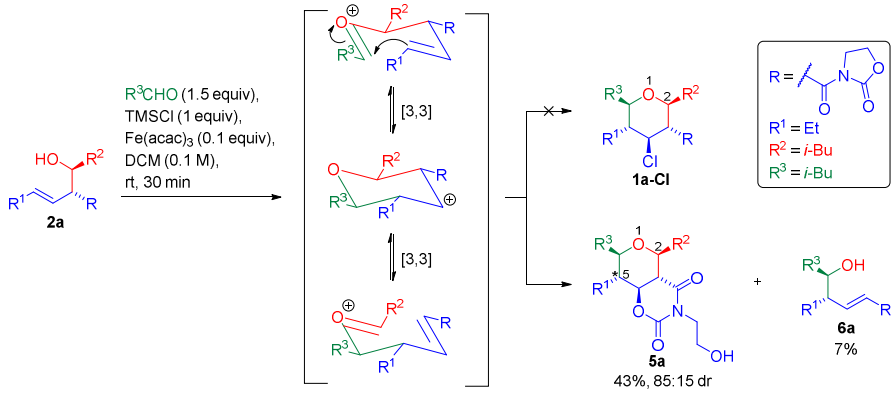
[a] 7.7 grams of product were obtained from 7 grams of **4a**. [b] It was isolated a 54% of an inseparable 2.5/1 mixture of the desired product β,γ-**3b** and its positional isomer *E*-α,β-**3b**. [c] Only *syn*-aldols were detected by ^{1}H NMR analysis of the reaction crudes, unless noted otherwise. [d] Traces of its diastereoisomer, *anti*-**2a**, were also isolated when a non-properly stored *n*-Bu_2BOTf was employed. [e] ^{1}H NMR analysis of the crude revealed that aldol **2g** was obtained as a 2/1 mixture of the *Z*- and *E*-isomers due to an isomerization of the double bond, although the yield given corresponds exclusively to the desired *Z*-isomer. [f] (2*S*,3*R*). [g] (2*R*,3*S*).

With aldols **2** in hand, we decided to test the Prins cyclization conditions previously optimized in our research group, employing the system $Fe(acac)_3$/TMSCl as

promoter.[22d] 4-Chloro-THP **1a-Cl** was selected as target molecule and aldol **2a** and isovaleraldehyde as starting materials (Scheme 2). The presence of each *i*-Bu in positions 2 and 6 of the ring should avoid the obtaining of undesired THPs as a consequence of the side chain exchange due to the 2-oxonia-Cope rearrangement, a [3,3]-sigmatropic rearrangement concomitant to the Prins cyclization.[41] Aldol **2a** yielded two products after 30 min, one of them more nonpolar than the substrate and the other one more polar and UV-visible. Regarding the nonpolar product, ^{1}H NMR analysis confirmed the presence of a THP ring with the expected side chains. However, mass analysis revealed that the molecule did not own a chlorine atom. Fortunately, X-ray crystallography unambiguously determined that the product was **5a**, in which the THP ring appeared fused to a 1,3-oxazinane-2,4-dione ring (Scheme 2). Thus, bicycle **5a** was obtained as a mixture of two diastereoisomers (85:15 dr) in 43% total yield. The X-ray analysis, together with the *J*-coupling over 9 Hz[42] and GOESY experiments,[43] allowed us to establish an all-*trans* configuration in the major diastereoisomer. GOESY experiments also revealed that the minor diastereoisomer was the C_5-epimer (Scheme 2). On the other hand, the polar product was obtained in 7% yield and identified as alcohol **6a**, a skeletal isomer of aldol **2a**, obtained on account of the 2-oxonia-Cope rearrangement (Scheme 2).[41] Once the products of the reaction were identified, we directed our attention to the unprecedented synthesis of the bicycle **5**. Rearrangements of *N*-acyl oxazolidin-2-ones to yield this kind of heterocycles had been previously reported,[44] though, to the best of our knowledge, this was the first example in which the 1,3-oxazinane-2,4-dione ring was fused with a THP. Additionally, it should be remarked that both heterocycles usually are related with varied biological activities such as anti-epileptic,[45] analgesic[46] and antiproliferative.[11] A synergistic biological activity might be expected from these structures. Despite of its unexpected bicyclic structure,

compound **5a** is a 2,3,4,5,6-pentasubstituted THP, so it consequently satisfies our initial synthetic goal (Scheme 1). Additionally, the uniqueness of this bicyclic core encouraged us to delve into the synthesis of this kind of compounds.

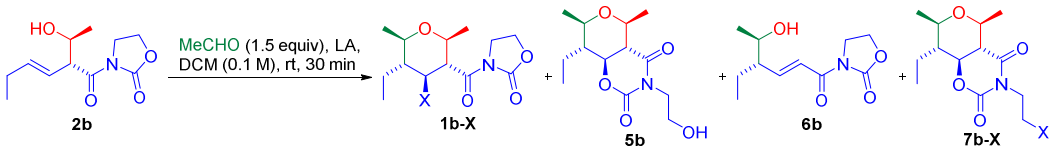
Scheme 2. Fe-Based Prins Cyclization of Aldol 2a to Yield Unexpected Bicycle 5a



We first screened a series of Lewis acids (LAs) to pursue better yields in the obtaining of bicycles **5**. We chose alcohol **2b** and MeCHO as the most simple starting materials to access to a 2,3,4,5,6-pentasubstituted THP (Table 2). Firstly, those reagents were submitted to the previously published conditions with $Fe(acac)_3$/TMSCl (Scheme 2),[22d] obtaining the expected bicycle **5b** as an only diastereoisomer with a similar yield to that of **5a** (38% vs 43%), together with traces of the undesired rearrangement isomer **6b** (Table 2, entry 1). A higher presence of $Fe(acac)_3$ improved the yield of **5b** and avoided the formation of **6b** (entries 2 vs 3). Nevertheless, when $Fe(acac)_3$ and TMSCl were employed separately as catalysts, the cyclization did not occur after 5 h of reaction. The yield of **5b** did not improve when an excess of $FeCl_3$ was employed as an alternative source of Fe(III) (entry 4), although a supra-stoichiometric quantity of $InCl_3$ led to **5b** with an interesting 61% yield (entry 5). When 0.1 equiv of those iron and indium compounds were tested, unaltered starting material was recovered. Other promoters were tested[47] until we discovered that $BF_3{\cdot}THF$ allowed the synthesis of **5b**

with a remarkable 70% yield, although with a higher proportion of **6b** (entry 6). To our delight, a better yield was obtained when $BF_3 \cdot OEt_2$ was chosen as the LA, and **6b** was not detected (entry 7). Almost the same yield was obtained when a larger amount of $BF_3 \cdot OEt_2$ was employed (entry 8), but when the amount of the LA was progressively reduced, the yield of **5b** decreased in favor of an increase in the yield of non-desired **6b** and longer reaction time (entries 9 and 10). Then, we decided to evaluate the combined effect of $BF_3 \cdot OEt_2$ with TMSCl as promoter of the EAP cyclization (entries 11-12). We repeated the reaction shown in the entry 10 (0.05 equiv of $BF_3 \cdot OEt_2$) including 2.5 equiv of TMSCl in the set of reagents. Surprisingly, under these conditions the main product of the reaction was the halogenated bicycle **7b-Cl** instead of the bicycle **5b** (entry 11). Additionally, it was also observed the obtaining of the rearranged alcohol **6b** together with part of the unreacted starting material. When the amount of the $BF_3 \cdot OEt_2$ was increased to 0.5 equiv, the starting aldol was consumed, yielding a 67% of **7b-Cl** along with traces of **6b** (entry 12). By contrast, when 2.5 equiv of TMSCl were employed as sole promoter, a practically equimolar mixture of the halogenated product **7b-Cl** and the starting material was detected after 44 h (entry 13). Next, we decided to check the influence of the halogen in this process. When TMSI was employed as promoter, full conversion of aldol **2b** was observed after only 10 min, and two products were identified (entry 14): the expected halogenated bicycle **7b-I** (58%) and the 4-iodine-THP **1b-I** (17%), with the originally pursued structure (Scheme 1). In the same vein, TMSBr allowed the access to **7b-Br** (46%) and **1b-Br** (30%) after 3 h of reaction (entry 15).[48] We eventually tested the EAP cyclization employing $FeBr_3$ both as a LA and as a bromide source. The reaction was complete after 30 min yielding the 4-bromo-THP **1b-Br** (23%), the hydroxylated bicycle **5b** (34%) and the rearranged alcohol **6b** (9%), but no traces of the halogenated bicycle **7b-Br** were detected (entry 16).

Table 2. Screening of Lewis Acids (LAs)



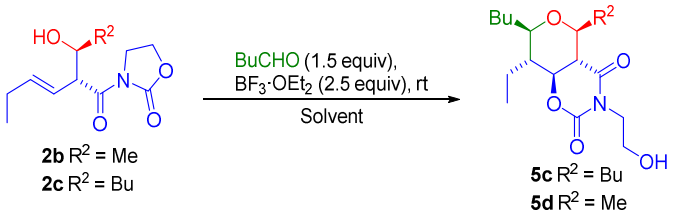
Entry	LA	Equiv	X	**1b-X** (%)[a]	**5b** (%)[a]	**6b** (%)[b]	**7b-X** (%)[a]
1	$Fe(acac)_3$/TMSCl	0.1/1.5	-	-	38	1	-
2[c]	$Fe(acac)_3$/TMSCl	0.5/1.5	-	-	59	-	-
3[d]	$Fe(acac)_3$/TMSCl	0.02/1.5	-	-	28	3	-
4	$FeCl_3$	1.5	-	-	41	2	-
5	$InCl_3$	1.5	-	-	61	15	-
6	BF_3·THF	2.5	-	-	70	13	-
7	BF_3·OEt_2	2.5	-	-	78	-	-
8	BF_3·OEt_2	5	-	-	79	-	-
9	BF_3·OEt_2	1	-	-	68	3	-
10[d]	BF_3·OEt_2	0.05	-	-	58	7	-
11[d,e]	BF_3·OEt_2/TMSCl	0.05/2.5	Cl	-	-	10	46
12[f]	BF_3·OEt_2/TMSCl	0.5/2.5	Cl	-	-	6	67
13[g]	TMSCl	2.5	Cl	-	-	6	45[b]
14[h]	TMSI	2.5	I	17	-	-	58
15[i]	TMSBr	2.5	Br	30	-	-	46

16	$FeBr_3$	2.5	Br	23	34	9	-

[a] Isolated yield, unless noted otherwise; >95:5 dr (determined by ^{1}H NMR spectroscopy). [b] Calculated by ^{1}H NMR spectroscopy. [c] The employment of 1 equiv of $Fe(acac)_3$ lead to a decrease in the yield of **5b** and to the obtaining of traces of **7b-Cl**. [d] The reaction was stopped after 20 h. [e] It was recovered a 44% of unreacted starting material. [f] The reaction was stopped after 2 h. [g] The reaction was stopped after 44 h and it was found a 49% of unreacted starting material. [h] The reaction was stopped after 20 min. [i] The reaction was stopped after 3 h.

Once verified the benefits of $BF_3{\cdot}OEt_2$ as promoter of the EAP cyclization, it was studied the effect of the solvent (Table 3). Bicycle **5c** was obtained as a sole diastereoisomer in 66% yield from aldol **2c** and *n*-pentanal employing DCM as solvent (entry 1). Secondly, the reaction was repeated several times replacing DCM by solvents such as acetonitrile, benzene and toluene, although the yield did not improve (entries 2-4). The crudes of those reactions were thoroughly studied by ^{1}H NMR to check that no by-products associated to competitive Prins-Ritter[49] or Prins-Friedel-Crafts[50] processes (both associated to nucleophilic solvents) were obtained. The selection of Et_2O as solvent led to the poorest yield (entry 5). Interestingly, when acetic acid was employed as solvent, bicycle **5c** was obtained as its *O*-acetylated derivative (entry 6). However, keeping the acetic acid as solvent and leaving out the $BF_3{\cdot}OEt_2$ as promoter, the reaction did not take place. It was also tested the Prins cyclization between aldol **2b** and *n*-pentanal employing DCM as solvent to access to bicycle **5d** in 69% yield (entry 7). There was a drop in yield when the reaction was repeated in the presence of $CHCl_3$ or *n*-hexane as solvents (entries 8-9).

Table 3. Screening of Solvents



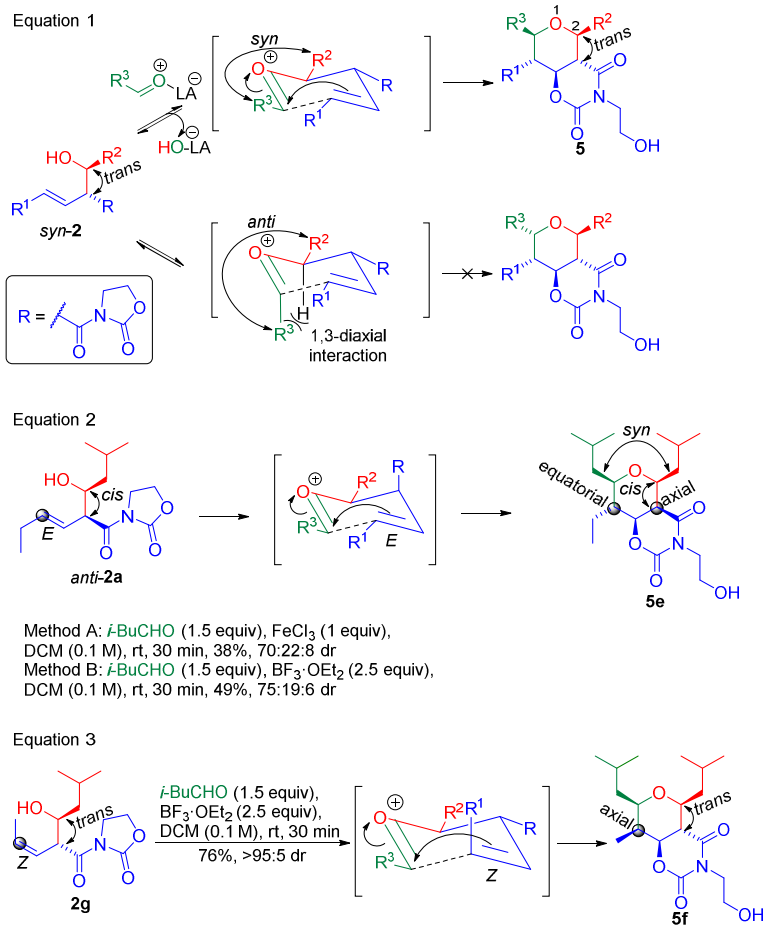
Entry	Aldol	Solvent	Bicycle	Yield (%)[a]
1	**2c**	DCM	**5c**	66
2	**2c**	Acetonitrile	**5c**	55
3	**2c**	Benzene	**5c**	52
4	**2c**	Toluene	**5c**	43
5	**2c**	Et_2O	**5c**	21
6[b]	**2c**	Acetic acid	**5c-Ac**	71
7	**2b**	DCM	**5d**	69
8	**2b**	$CHCl_3$	**5d**	50
9	**2b**	*n*-hexane	**5d**	31

[a] Isolated yield; >95:5 dr (determined by ^{1}H NMR spectroscopy). [b] Bicycle was obtained as its *O*-acetylated derivative.

The studies described above allowed us to conclude that the optimized conditions for the EAP cyclization imply the use of 2.5 equiv of $BF_3{\cdot}OEt_2$ and DCM as solvent at rt.[51] This EAP cyclization has proven to be a diastereoselective fashion to synthesize 2,3,4,5,6-pentasubstituted THPs with an all-*trans* stereochemistry, placing their substituents in equatorial positions. The substituents at C_2 and C_6 of the THP adopt a preferred *syn* stereochemistry to minimize the 1,3-diaxial interaction in the chair-like transition state (Scheme 3, equation 1).[52] The position of the oxygen atom linked to C_4

is a consequence of the position adopted by the oxazolidin-2-one in the transition state, as will be discussed in the mechanistic discussion section (Scheme 7). Regarding the stereochemistry of C_3 and C_5, it is controlled by the stereochemistry of the starting alcohol. On the one hand, the *trans* disposition of the substituents of the *syn*-aldol[31] leads to the *trans* orientation of the substituents at C_2 and C_3 (equation 1 and 3); by contrast, an *anti*-aldol should conduct to a *cis* orientation of those substituents (equation 2). On the other hand, an *E*-geometry of the olefin conducts to the equatorial position of the substituent at C_5 (equations 1 and 2), whereas a *Z*-geometry should favor the axial position (equation 3). A further mechanistic discussion will be given in Scheme 7.[26] As we had obtained a small amount of *anti*-**2a** (Table 1, entry 7), we decided to evaluate it in the EAP cyclization to synthesize the bicycle **5e** with the substituent at C_3 in an axial position (Scheme 3, equation 2). Thus, *anti*-**2a** was submitted to each reactions employing $FeCl_3$ (method A) and $BF_3{\cdot}OEt_2$ (method B) as Lewis acids. In both cases, the main product was the expected bicycle **5e**, whose relative stereochemistry was confirmed by GOESY analysis. However, the employment of the *anti*-**2a** as starting material yielded the synthesis of two undesired minor diastereoisomers in 3/1 proportion: the main one was identified as the all-*trans* bicycle **5a**, whereas the other one was its C_5-epimer.[53] When *syn*-aldol **2g**, bearing a *Z*-olefin, was submitted to the optimized EAP cyclization conditions, the desired bicycle **5f** was diastereoselectively obtained in 76% yield (Scheme 3, equation 3). As bicycles **5e** and **5f**, bearing axial substituents, can be accessed via the EAP cyclization, it therefore constitutes an interesting tool to access to the core of natural products such as kendomycin or phorboxazols (Figure 1).

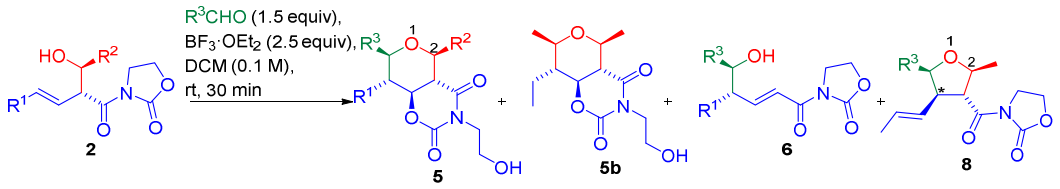
Scheme 3. Synthesis of Bicycles with Different Stereochemical Patterns

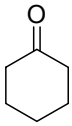


Afterwards, we selected *syn*-aldol **2b** as starting material to check the robustness of the optimized conditions ($BF_3{\cdot}OEt_2$/DCM/rt) by broadening the scope of aldehydes (Table 4). Entries 1 and 2 collect the previously described synthesis of bicycles **5b** (Table 2, entry 7) and **5d** (Table 3, entry 7), respectively. Besides these linear chains, the bulkier *i*-Bu was successfully introduced at the C_6 position of the THP yielding a 70% of **5g** (entry 3). Hex-5-ynal and pent-4-ynal were synthesized through a PCC-mediated oxidation of the corresponding commercial alcohols,[54] and they were employed in the Prins cyclization without further purification, yielding bicycles **5h** and **5i** respectively (entries 4 and 5). Together with **5i**, it was detected a small amount of bicycle **5b** because of the release of MeCHO to the medium as result of the 2-oxonia-Cope rearrangement.[41] We also chose oct-2-ynal to test an α,β-unsaturated

aldehyde, and bicycle **5j** was obtained in 46% yield (entry 6). It should be noted that oct-2-ynal protected as its diethylacetal led to the same product with a slightly inferior 39% yield. Cyclopropanecarbaldehyde is an apparently problematic aldehyde due to presence of an acid-sensitive motif,[55] but to our delight it reacted properly to yield **5k** in 63% yield (entry 7). Cyclohexanone was also tested as carbonylic compound in the EAP cyclization to study the obtaining of spirotetrahydropyrans,[56] providing **5l** in 23% yield although with excellent diastereoselectivity (entry 8). The low yield is a consequence of the influence of the 2-oxonia-Cope rearrangement, which leads to the obtaining of bicycle **5b** as the main product. Additionally, the 2,3,4,5,5-pentasubstituted tetrahydrofuran (THF) **8l** was isolated as a 4/1 mixture of the epimers at C_4 in 19% yield. It is proposed that THF **81** is a consequence of a 5-*exo-trig* attack of the olefin on the oxocarbenium ion,[57] instead of the 6-*endo-trig* attack conducive to the bicycle **5**. Afterwards, benzaldehyde (entry 9) and several electron-poor aromatic aldehydes (entries 10-12) were evaluated. An electron-rich aromatic aldehyde carrying a MeO group in *para*- position also provided a similar good yield (entry 13), though a drop in the yield was observed when the same donor group was located in the *orto*- position (entry 14).[58] As occurred when cyclohexanone was employed as carbonylic compound (entry 8), the corresponding 2,3,4,5-tetrasubstituted THFs **8** were generally identified (entries 9-11 and 13-14), unlike the results found when aliphatic aldehydes were used as starting materials.

Table 4. Synthesis of Differently Substituted THPs



Entry	**2**	R^1	R^2	R^3	**5** (%)[a]	**5b** (%)[b]	**8** (%)[c]
1	**2b**	Et	Me	Me	**5b** (78)	78	-
2	**2b**	Et	Me	Bu	**5d** (69)	-	-
3	**2b**	Et	Me	*i*-Bu	**5g** (70)	-	-
4	**2b**	Et	Me	$HC{\equiv}C(CH_2)_3$	**5h** (65)	-	-
5	**2b**	Et	Me	$HC{\equiv}C(CH_2)_2$	**5i** (60)	10	-
6	**2b**	Et	Me	n-$C_5H_{11}C{\equiv}C$	**5j** (46)[d,e]	-	-
7	**2b**	Et	Me	c-Pr	**5k** (63)	-	-
8	**2b**	Et	Me		**5l** (23)	45	**8l** (19)
9	**2b**	Et	Me	Ph	**5m** (72)	-	**8m** (4)
10	**2b**	Et	Me	3-F-Ph	**5n** (64)	-	**8n** (8)[f]
11	**2b**	Et	Me	2-Cl-Ph	**5o** (60)	1	**8o** (16)
12	**2b**	Et	Me	4-Br-Ph	**5p** (68)	3	-
13	**2b**	Et	Me	4-(MeO)-Ph	**5q** (63)	12	**8q** (10)
14	**2b**	Et	Me	2-(MeO)-Ph	**5r** (20)	10	**8r** (20)
15[g]	**2a**	Et	*i*-Bu	*i*-Bu	**5a** (75)	-	-
16	**2c**	Et	Bu	Bu	**5c** (66)	-	-
17[g]	**2c**	Et	Bu	*i*-Bu	**5s** (50)	-	-

18	**2d**	Et	Ph	Me	**5t** (35)[d]	55	-
19	**2h**	Et	4-Br-Ph	Me	**5u** (43)	6	-
20	**2e**	Et	$PhCH_2CH_2$	Me	**5v** (54)[d]	-	-
21[h]	**2f**	H	Me	Me	**5w** (38)	-	-
22[i]	**2f**	H	Me	Ph	**5x** (39)[d]	-	-
23[j]	**2f**	H	Me	3,4-$(MeO)_2$Ph	**5y** (41)	-	-

[a] Isolated yield; >95:5 dr, unless noted otherwise (determined by ^{1}H NMR spectroscopy). [b] Calculated by ^{1}H NMR spectroscopy, except in entry 1, where **5b** is the expected product. [c] Isolated yield; 80:20 dr, unless noted otherwise (determined by ^{1}H NMR spectroscopy). [d] 90:10 dr (determined by ^{1}H NMR spectroscopy). [e] A 39% yield was obtained when aldehyde was employed protected as diethylacetal. [f] 85:15 dr (determined by ^{1}H NMR spectroscopy). [g] Reaction performed at 0 ºC. [h] 40% of **6b** was also isolated; when *n*-hexane (0.05 M) was employed as solvent, 50% of **5w** and 30% of **6b** were isolated. [i] **6x** (35%) and **5w** (14%, >95:5 dr) were calculated by ^{1}H NMR spectroscopy. [j] **6y** (10%) and **5w** (14%, >95:5 dr) were calculated by ^{1}H NMR spectroscopy.

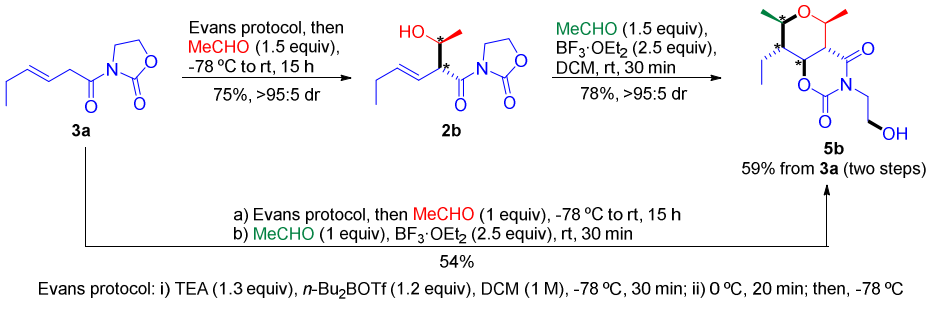
Once the effectiveness of the Prins cyclization between the simplest secondary aldol **2b** (R^2 = Me) and several aldehydes R^3CHO was demonstrated, we decided to modify both substituents R^2 and R^3 (Table 5). As illustrated in entry 15, when $R^2 = R^3$ = *i*-Bu, bicycle **5a** was efficiently synthesized as a sole diastereoisomer performing the reaction at 0 ºC (traces of the C_5-epimer were obtained when the reaction was carried out at rt). Entry 16 gathers the previously discussed synthesis of bicycle **5c** (Table 3, entry 1). When the synthesis of bicycle **5s** was addressed, it was essential performing the reaction at 0 ºC to avoid the obtaining of traces of the bicycles **5a** and **5c**, as consequence of the processes associated to the 2-oxonia-Cope rearrangement (entry 17).[41] However, when MeCHO was combined with **2d** (R^2 = Ph), the presence of an aromatic group directly attached to the hydroxy group of the aldol led us inevitably to a

mixture of the desired bicycle **5t** (35%) and side chains exchanged by-product **5b** (55%) as main product (entry 18). This phenomenon can be explained considering that if R^2 is an aromatic group, it stabilizes by resonance the intermediate oxocarbenium obtained after the 2-oxonia-Cope rearrangement.[59] As expected, the presence of an electron withdrawing group in the aromatic moiety of aldol **2h** (R^2 = 4-Br-Ph) conducted to a decrease of the undesired by-product **5b** and yielded bicycle **5u** diastereoselectively (entry 19).[60,61] The presence of a two-unit methylene bridge between the aromatic and the hydroxy groups of the aldol **2e** ($R^2 = PhCH_2CH_2$) allowed likewise an improvement of the yield in the synthesis of bicycle **5v** (entry 20). Then we tested the EAP cyclization employing aldol **2f** (R^1 = H) as starting material. When it was combined with MeCHO, the absence of an aliphatic chain attached to the olefin led to the bicycle **5w** in 38% yield (entry 21), significantly lower than the 78% obtained during the synthesis of **5b** (R^1 = Et, entry 1). Moreover, the 2-oxonia-Cope by-product **6c** (R^1 = H, R^3 = Me) was also isolated in 40% yield, the highest one of all the examples shown up to now.[62] This result will be addressed again at the end of the mechanistic section (Scheme 7). Similar results were found when aldol **2f** was combined with aromatic aldehydes to yield bicycles **5x** and **5y**, and in these cases traces of bicycle **5w** (entries 22 and 23) were also isolated. In spite of the low yield, it should be remarked that 2,3,4,6-tetrasubstituted THPs **5w**, **5x** and **5y** bear their substituents in equatorial positions, hence they share the same core shown by natural products such as polycavernosides and clavosolides (Figure 1), which enhance the synthetic utility of the EAP protocol.

Summarizing, this EAP protocol allows the two-steps conversion of *N*-acyl oxazolidin-2-ones **3** into bicycles **5** via the formation of aldols **2**. During the first step, the Evans aldol methodology permits the generation of a σ C-C bond and two stereocenters in a diastereoselective fashion. The Prins cyclization of those aldols

implies the creation of four σ bonds (three C-O and one C-C) and the insertion of three stereocenters (Scheme 4, new bonds are highlighted in bold and the stereocenters with asterisks). Therefore, starting from a molecule with no chiral centers such as **3a**, a high structural complexity may be straightforwardly generated: bicycle **5b** was obtained in 59% yield as a single diastereoisomer after just two steps. Nevertheless, we wondered if an even simpler alternative could be performed, by combining both Evans aldol and Prins cyclization in a one-pot process. Thus, *N*-acyl oxazolidin-2-one **3a** and MeCHO were submitted to the Evans protocol to yield **2b**; once TLC analysis showed that the reaction was complete, another portion of MeCHO and 2.5 equiv of $BF_3{\cdot}OEt_2$ were added to the reaction medium (Scheme 4). To our delight, bicycle **5b** was obtained in 54% yield, comparable to that obtained in the two-steps process. It should be empathized that this is a truly excellent yield for a method in which five contiguous stereocenters are diastereoselectively installed and five σ bonds are generated, meaning an average yield for each bond of 88%. Additionally, this simplified protocol avoids the work-up and purification of aldol **2b**, with the consequent saving of organic solvents and time.

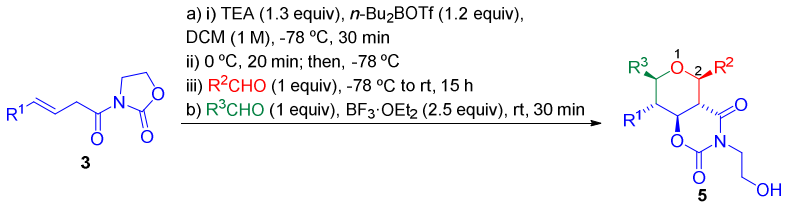
Scheme 4. Two-steps EAP Cyclization vs One-pot EAP Cyclization



The efficacy of the one-pot EAP protocol in the synthesis of **5b** encouraged us to expand the scope by combining several *N*-acyl oxazolidin-2-ones **3** and diverse aldehydes (Table 5). Entry 1 gathers the result previously shown in Scheme 4. *N*-acyl

oxazolidin-2-one **3a** also yielded bicycles **5** bearing different aliphatic and aromatic groups at C_2 and C_6 (entries 2-5). Entry 6 shows that this one-pot EAP protocol was perfectly compatible with a multigram synthesis, allowing the preparation of 5.3 g of bicycle **5a** from **3a** with no loss of yield and enhancing the synthetic utility of this methodology. The one-pot EAP protocol was also efficient starting from *N*-acyl oxazolidin-2-ones bearing an aromatic group (entry 7) and longer linear aliphatic chain (entries 8 and 9). When a benzyl ether was present at starting material **3f**, the corresponding bicycle was achieved in 54% overall yield, as a 1.3/1 mixture of the benzylated/non-benzylated product (entry 10).

Table 5. Synthesis of 2,3,4,5,6-Pentasubstituted THPs via the One-pot EAP Cyclization



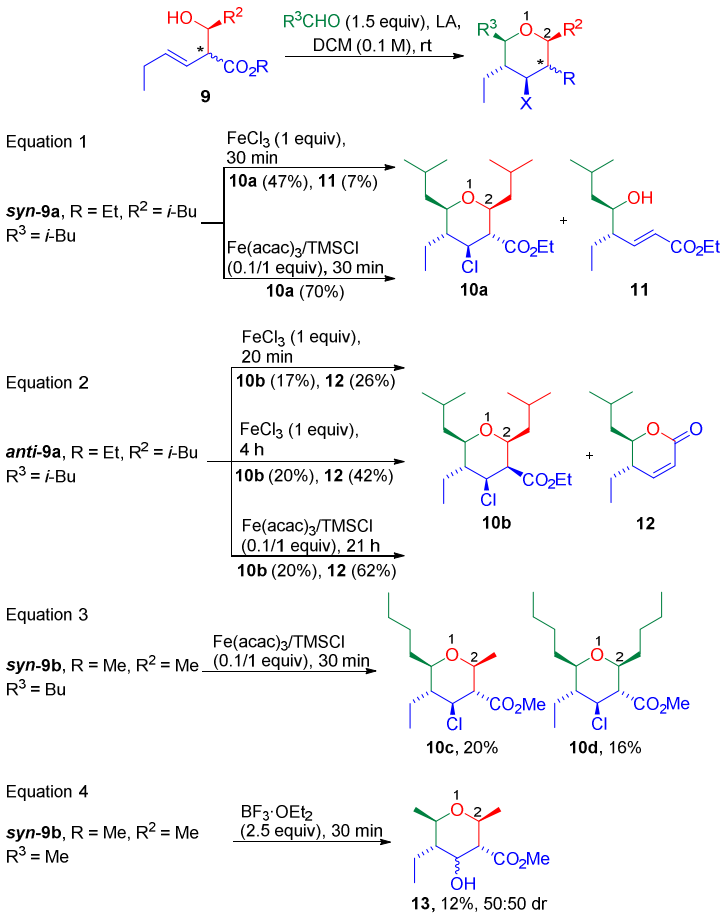
Entry	Substrate	R^1	R^2	R^3	Bicycle	Yield (%)[a]	$Yield_{av}$ (%)[b]
1	**3a**	Et	Me	Me	**5b**	54	88
2	**3a**	Et	4-Br-Ph	Me	**5u**	22[c]	74
3	**3a**	Et	*n*-$C_{13}H_{27}$	Me	**5z**	41	84
4	**3a**	Et	*i*-Bu	Me	**5aa**	42	84
5	**3a**	Et	Bu	Ph	**5ab**	31[d]	79
6	**3a**	Et	*i*-Bu	*i*-Bu	**5a**	60[e]	90

7	**3d**	$PhCH_2$	Bu	Bu	**5ac**	32	80
8	**3e**	*n*-pentyl	Me	Bu	**5ad**	31	79
9	**3e**	*n*-pentyl	Bu	Me	**5ae**	30	79
10	**3f**	$BnOCH_2CH_2$	Me	Me	**5af**	54[f]	88

[a] Isolated yield; >95:5 dr, unless noted otherwise (determined by ^{1}H NMR spectroscopy). [b] Average yield of each one of the five new σ-bonds generated during the one-pot EAP cyclization. [c] It was also isolated **5b** (4%, >95:5 dr). [d] 90:10 dr (determined by ^{1}H NMR spectroscopy). [e] 5.3 grams were obtained with 85:15 dr. [f] Obtained as a 1.3/1 mixture of the benzylated/non-benzylated THPs.

In summary, both in the two-steps and the one-pot versions, the EAP protocol rises up as a powerful tool for the synthesis of valuable 2,3,4,5,6-pentasubstituted THPs with the general structure **5**. However, in spite of its contrasted efficacy, we still kept in mind our original aim of accessing to densely substituted 4-halo-THPs **1** (Scheme 1). During the above-related studies through the understanding of the EAP cyclization, the isolated synthesis of such 4-halo-THPs (Table 2, entries 14-16) really grabbed our attention, because those were the only examples in which the oxazolidin-2-one moiety acted as a mere spectator instead of undergoing a rearrangement to form the bicyclic structure. For this reason, we were interested in studying the influence of the nature of the substituent directly attached to the carbonyl group in the aldol employed as starting material in the Prins cyclization (Scheme 5).

Scheme 5. Influence of the Nature of the Substituent Directly Attached to the Carbonyl Group



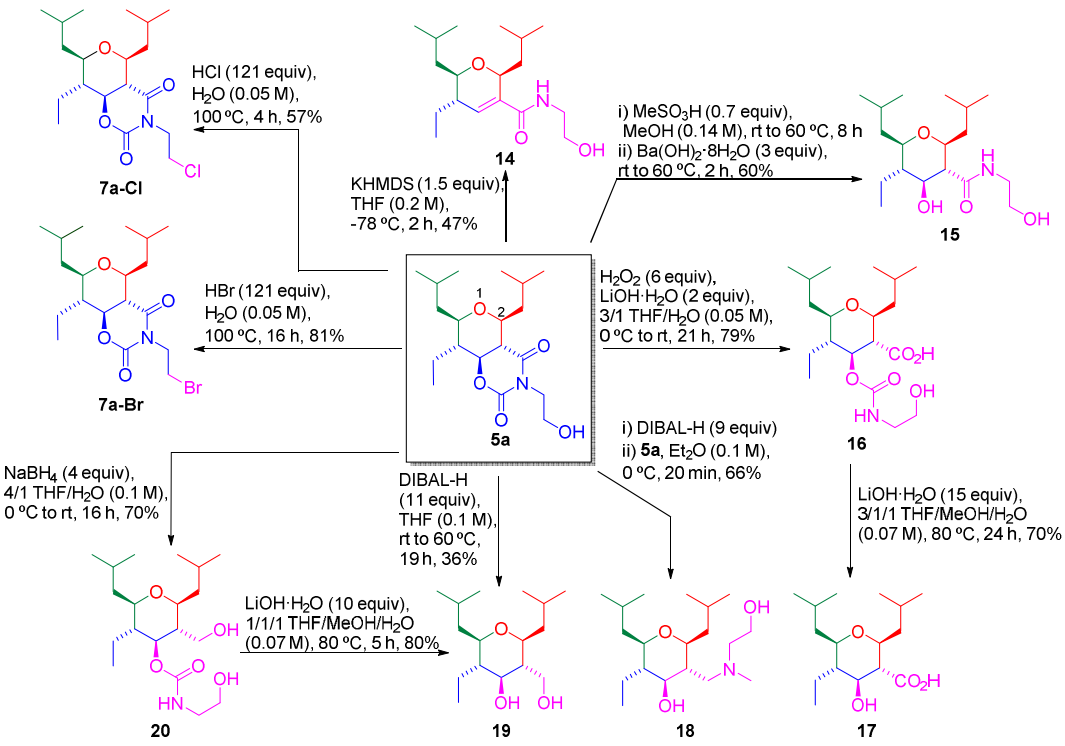
Thus, we devised a variation of the aldol-Prins cyclization with aldols **9a** and **9b**, whose structures are identical to Evans aldols **2a** and **2b** except for the substitution of the oxazolidin-2-one moiety for an ester group. *syn*-Aldol **9a** was combined with *i*-BuCHO in a Prins cyclization promoted by $FeCl_3$ to produce 4-chloro-THP **10a** in 47% yield (equation 1, top). The isolation of a small amount of homoallylic alcohol **11** (7%) demonstrated that the Prins cyclization was competing with the 2-oxonia-Cope rearrangement. Fortunately, the generation of this undesired by-product was suppressed when the promoter system was replaced by $Fe(acac)_3$/TMSCl, allowing the synthesis of **10a** in 70% yield (equation 2, bottom). *anti*-Aldol **9a** was also submitted to this Fe-based Prins cyclization to evaluate the influence of the stereochemistry present in the starting material (equation 2). The reaction was firstly stopped at 20 min and the nonpolar product analysed by NMR, revealing the expected 4-chloro-THP **10b** (17%),

the C_3-epimer of **10a**, whose stereochemistry was unequivocally assigned based on the GOESY analysis and the *J*-coupling values found (equation 2, top). When the presumed remaining starting material was checked by NMR, we surprisingly discovered that it was actually a mixture of the unreacted *anti*-aldol **9a** (44%) and the δ-lactone **12** (26%). When the reaction time was increased to 4 h it was obtained a similar yield of THP **10b** (20%), although a higher proportion of lactone **12** (42%) regarding the unreacted starting aldol (10%) was detected (equation 2, middle). Eventually, when the system $Fe(acac)_3$/TMSCl was employed as promoter and the reaction time was set at 21 h, the starting material was completely consumed and lactone **12** was isolated in 62% yield, although the yield of THP **10b** did not improve (equation 2, bottom).[63] Next, we decided to evaluate the efficacy of Fe-based Prins cyclization for synthesizing THPs with different chains at the positions 2 and 6. Thus, *syn*-aldol **9b** was combined with BuCHO and treated with $Fe(acac)_3$/TMSCl (equation 3). Unfortunately, expected THP **10c** was obtained with a poor 20% yield together with a 16% of THP **10d**, in which a side chains exchange occurred as consequence of the 2-oxonia-Cope rearrangement. *syn*-Aldol **9b** was also submitted to the Prins cyclization mediated by 2.5 equiv of $BF_3 \cdot OEt_2$ pursuing the synthesis of the 4-hydroxy-THP **13** (equation 4). In contrast to the efficient synthesis of **5b** achieved when the analogous *syn*-aldol **2b** was treated under the same conditions (78% and >95:5 dr, see Table 4, entry 1), herein the desired THP **13** was obtained in 12% yield and as an 1/1 epimeric mixture at C_4. Thus, according to these results, the oxazolidin-2-one moiety directly attached to the carbonyl group of the aldol seems to be crucial, not only to guarantee the prevalence of the Prins cyclization product facing the 2-oxonia-Cope by-products, but also to achieve the THPs with good yields and diastereoselectivities.

Prins cyclizations illustrated in Scheme 5 constitute an unsuccessful pathway to yield desired 2,3,4,5,6-pentasubstituted THPs differently functionalized at C_3 and C_4, which are interesting intermediates for the synthesis of THP-containing natural products. However, the EAP protocol provides an efficient and robust access to this kind of THPs, although fused to a 1,3-oxazinane-2,4-dione ring (**5**). Thus, the removal of this second heterocycle should be an alternative way to access to highly substituted non-bicyclic THPs, such as those commonly found in natural products (Figure 1). Bicycle **5a** was chosen as starting material, and the cleavage of the nitrogenated heterocycle was tackled through different transformations (Scheme 6). Firstly, **5a** was refluxed with a HCl aqueous solution for 4 h; under these conditions, the bicyclic structure remained stable, although a chlorine atom replaced the terminal hydroxy group, yielding the halo-bicycle **7a-Cl** in 57% yield. The homologous product **7b-Cl** had been previously obtained with a similar yield when aldol **2a** was submitted to the Prins cyclization mediated by the system $BF_3{\cdot}OEt_2$/TMSCl (67%, see Table 2, entry 12). Similarly, when **5a** was refluxed with a HBr aqueous solution, the halo-bicycle **7a-Br** was obtained in 81% yield. Bicycle **5a** was also submitted to an elimination reaction by treatment with KHMDS in order to obtain the dihydropyran **14** with an amide at C_3.[64] That elimination reaction allowed the release of a CO_2 molecule to permit the cleavage of the bicyclic structure. Another protocol to transform bicycle **5a** into an amide was tested, affording a simple access to the β-hydroxy amide **15**.[65] Afterwards, a basic hydrolysis protocol was tried to yield a THP embedded in a β-hydroxy acid.[66] Thus, treatment of **5a** with freshly prepared lithium hydroperoxide yielded the THP **16** with a carboxylic acid at C_3 and a carbamate at C_4, which was successfully hydrolyzed at reflux with LiOH to allow the access to the β-hydroxy acid **17**. Eventually, several reductive protocols with DIBAL-H were analysed, observing noteworthy differences

according to the reagent nature and the addition order. When bicycle **5a** was added over an ice-cooled DIBAL-H solution, 4-hydroxy THP **18**, bearing a tertiary amine, was obtained because of the total reduction of both carbonyl groups. However, when DIBAL-H was dropwise added to a solution of bicycle **5a** in THF and then refluxed, diol **19** was obtained.[67] The employment of $NaBH_4$ as the source of hydride led to carbamate **20**,[68] whose hydrolysis yielded diol **19**.[66] The conclusion deduced from this derivatization screening is that bicycles **5**, easily obtained via our EAP protocol, constitute a versatile platform to access to a substantial family of highly substituted THPs bearing various functional groups.

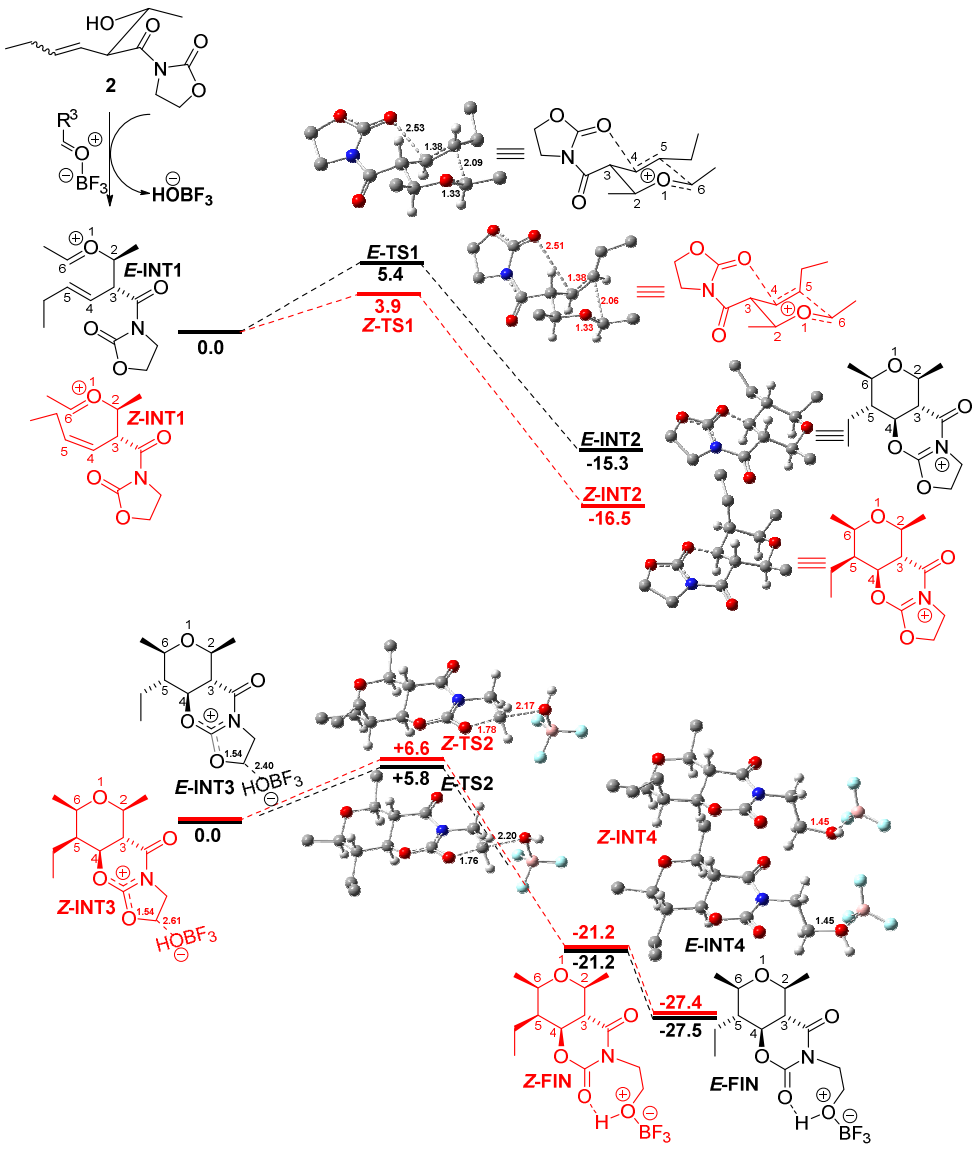
Scheme 6. Derivatization of Bicycles 5



A mechanistic model for the Prins cyclization using the *E*- and *Z*-homoallylic alcohols **2** obtained from the Evans aldol addition is outlined below. Considering that the variation of the reaction temperature almost did not affect the diastereoselectivity of the reaction and only modified the reaction time,[51] a kinetically controlled mechanism

would be expected. In addition, from the experimental results, it seems that the oxazolidin-2-one group is not a mere spectator in the process, since the reaction fails when it is replaced by an ester group (Scheme 5). We carried out DFT calculations to delve into the complete diastereoselectivity of the above-described Lewis acid-catalyzed Prins cyclization. In this regard, we computed the reaction profile (SCRF(CH_2Cl_2)-B3LTP/6-31g(d) level) involving the oxocarbenium resulting of the condensation of simple allylic alcohol **2b** (R^1 = Et, R^2 = Me) for both *E*- and *Z*-isomers (***E*-INT1** and ***Z*-INT1**) in the presence of BF_3 as the Lewis acid (Scheme 7). We speculate the formation of trifluorohydroxyborate from the BF_3 used, a species which will be important during the overall mechanism conducting to the final tetrahydropyran. Relative enthalpies ΔG (298 K) and bond distances are given in kcal/mol and angstrom, respectively. Numbering of the figures is arbitrary and used for discussion. Only representative hydrogens are shown. DFT calculations, in gas phase, were performed at the B3LYP/6-31G (d) level, punctual corrected to include solvation in DCM, using the SCRF method, used by default in Gaussian. The transition states were confirmed with the corresponding force calculations, ensuring the presence of a single imaginary frequency in all cases. For the determination of the ***E*-INT3** and ***Z*-INT3** complexes, the Basis Set Superposition Error was taken into account using the "counterpoise" method.

Scheme 7. Computed Reaction Profile for the Cyclization of Oxonium *E*-INT1 and Oxonium *Z*-INT1



We first discuss the cyclization for the *E*-isomer of the double bond at the homoallylic alcohol. As depicted in Scheme 7, oxonium ion ***E*-INT1** evolves exothermically (ΔE_r = –15.3 kcal/mol) to carbocation ***E*-INT2** through double bond nucleophilic attack. The transition state ***E*-TS1** (ΔE_r = +5.4 kcal/mol) adopts a chair-like conformation caused by the arrangement of the *N*-acyl oxazolidin-2-one bearing in the substrate. In this transition state, all substituents are located in the equatorial position setting the relative configurations of C_5 and C_6 in the product. The obtained carbocation, via ***E*-TS1**, allows the carbonyl nucleophilic equatorial attack of the oxazolidin-2-one

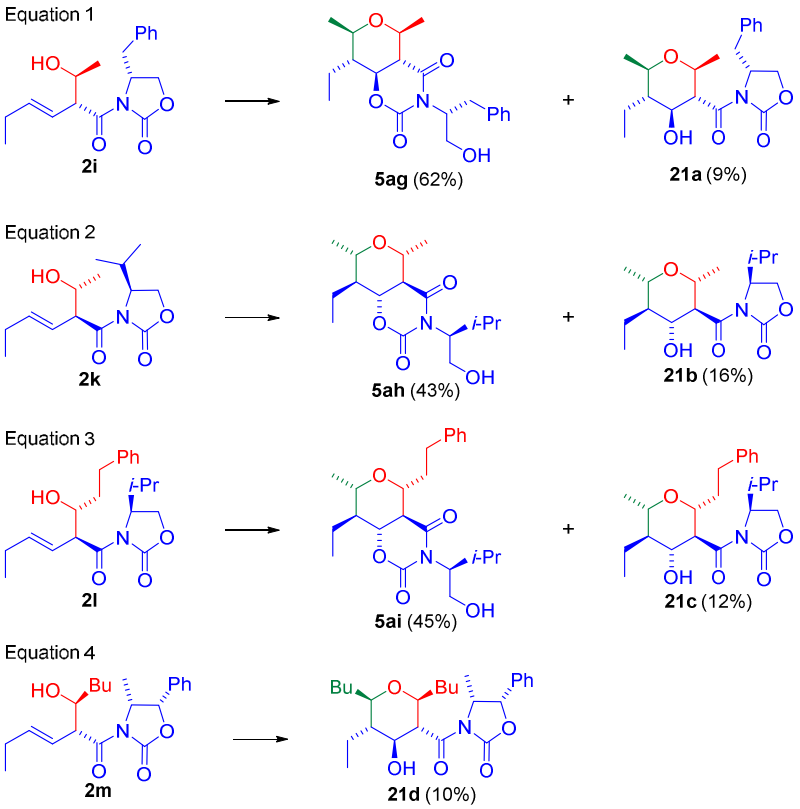
ensuring the stereochemistry at C_4 in ***E*-INT2**. This step is highly exothermic ($\Delta E_r = -15.3$ kcal/mol) as the result of the stabilization of the positive charge by the adjacent heteroatoms. The existence of a true bond between the oxazolidin-2-one carbonyl oxygen and the electron deficit center (numbered as 4 in the scheme), shown with a dotted line, was confirmed by the AIM (Atom in Molecules) methodology (6- 311 + g (d, p), // B3LYP / 6-31G (d)) which justifies the stereochemistry of this center. In a similar manner, the double bond nucleophilic attack to the electrophilic position in ***Z*-INT1** generates cyclic tetrahydropyran ***Z*-INT2** in an exothermic process ($\Delta E_r = -16.5$ kcal/mol). Transition state ***Z*-TS1** ($\Delta E_r = +3.9$ kcal/mol) adopts again a chair-like conformation locating the ethyl group in a pseudo axial position. The obvious consequence of this location is the resulting geometry at the C_5 position yielding the diastereoisomer ***Z*-INT2**, as it was observed experimentally (Scheme 3, equation 3). The reaction ends with an S_N2 nucleophilic attack of the trifluorohydroxyborate (formed during the condensation reaction) generating the primary alcohol and the corresponding 1,3-oxazinane-2,4-dione as the leaving group. We first performed calculations over the Van der Walls complex ***E*-INT3** having its origin from *E*-isomer of the double bond at the homoallylic alcohol. This process is highly exothermic yielding ***E*-INT4** ($\Delta E_r = -21.2$ kcal/mol) through a low computed activation barrier ***E*-TS2** ($\Delta E_r = +5.8$ kcal/mol). The lineal intermediate ***E*-INT4** evolves to the more stable and final BF_3-complex ***E*-FIN** stabilized by an intramolecular O···HO hydrogen bond. An experimental confirmation of this last S_N2 nucleophilic attack is provided for the formation of the corresponding acetate when acetic acid was used as a solvent, presumably via the formation of a $BF_3 \cdot HOAc$ complex (Table 3, entry 6).[69] As expected, calculations over the *Z*-isomer ***Z*-INT3** provides almost identical results as the *E*-isomer, providing exothermically ***Z*-INT4** ($\Delta E_r = -21.2$ kcal/mol) via the low energy

transition state ***Z*-TS2** (ΔE_r = +6.6 kcal/mol). In a similar manner, the reaction ends with the intramolecular formation of an H-bond in the final THP-complex ***Z*-FIN**. Thus, the Scheme 7 justifies the formation of the bicyclic compounds **5**, ratifying the experimental results. However, it was surprising that when we started from aldol **2f** bearing a terminal alkene (R^1 = H), the 2-oxonia-Cope products were observed in a significant way (Table 4, entries 21-23). In order to find a theoretical justification of this phenomenon, we proceeded to repeat the same calculations shown in Scheme 7 for R^1 = H, also generating a reaction coordinate from the approach C_5-C_6. We observed that in the product equivalent to ***E*-INT1** (or ***Z*-INT1**), the hypothetical carbocation at C_4 is not assisted by the carbonyl of the oxazolidin-2-one. In theses cases, the approaching leads directly to the rearranged product **6** (ΔE_r = –9.0 kcal/mol and ΔE_r*= 3.0 kcal/mol). Clearly, the substitution of the terminal vinyl position in aldols **2** ($R^1 \neq$ H) stabilizes the charge at C_4 to induce the approximation of the oxazolidin-2-one ring, favoring the formation of the tricyclic intermediate ***E*-INT2** or ***Z*-INT2** (Scheme 7). Otherwise the [3,3]-sigmatropic rearrangement is observed.

To extend the applicability of the EAP cyclization, the enantiomeric version was tested employing the chiral alcohols **2i-m** previously obtained (Table 1, entries 18-22).[70] Thus, Prins cyclization of acetaldehyde and aldol **2i**, bearing a benzyl group in the oxazolidin-2-one, allowed the obtaining of the expected bicycle **5ag** in 62% yield, but also led to the unprecedented isolation of THP **21a** in 9% yield (Scheme 8, equation 1).[71] THPs as **21** (referred as THP-Xc to highlight the presence of the non-rearranged oxazolidin-2-one in their structures) were not detected in any of the Prins cyclizations previously studied, therefore it was reasoned that the chiral nature of the oxazolidin-2-one motif was involved in their generation. In an attempt to control the relative amount of isomers **5** and **21**, a screening of Lewis acids was unsuccessfully perfomed.[72]

However, it must be pointed out that, from a synthetic point of view, the presence of this pair of products is not a handicap since under hydrolysis or reduction conditions both must evolve to the same 2,3,4,5,6-pentasubstituted THP (see products **17** and **19** in Scheme 6). When the Prins cyclization was carried out employing acetaldehyde and aldol **2k**, in which the oxazolidin-2-one presents an *i*-Pr group instead of a benzyl group, both the bicyclic product **5ah** (43%) and the THP-Xc **21b** (16%) were obtained again, as reflected in equation 2. In a similar manner, cyclization using aromatic alcohol **2l** provided a mixture of bicycle **5ai** and THP-Xc **21c** in 57% overall yield (equation 3). Finally, we decided to study the Prins cyclization between *n*-pentanal and aldol **2m**, in which the oxazolidin-2-one motif presents substituents on both positions adjacent to N and O (equation 4). THP-Xc **21d** was obtained with an apparently disappointing 10% yield, though this result is really meaningful from the mechanistic point of view. As shown in Scheme 7, the nucleophilic attack of the trifluorohydroxyborate to the position adjacent to the O of the oxazolidin-2-one usually leads to the generation of bicycles **5**. Nevertheless, in this case the presence of the phenyl substituent in that position prevents the nucleophilic attack over the oxazolidin-2-one, yielding exclusively a THP-Xc **21**.

Scheme 8. Prins Cyclization of Enantiomeric Aldols[a]



[a] Reaction conditions: MeCHO (1.5 equiv), Lewis acid, DCM (0.1 M), rt, 30 min. All products were obtained with >95:5 dr except **5ah** (92:8 dr).

Eventually, many of all these new products were biologically evaluated. Our interest in the development of bio-studies concerning THPs arises from the high incidence of this structural motif in bioactive natural products (Figure 1) and from their inherent bioactivity. As antimicrobial and antifungal activities are recurrently associated to THPs,[4,5,8,9,13] we decided to evaluate the antimicrobial activity to 33 of the compounds obtained in the current study[73] against gram-positive and gram-negative bacteria and the yeast *C. albicans*. The MIC_{50} values listed in Table 6 clearly show that the effect of the compounds is limited to Gram positive bacteria. *B. subtilis* was more sensitive than genus *Staphylococcus,* although the compounds **5c** and **5ad** displayed activity against *S. aureus* methicillin resistance (MIC_{50} 28 μg/mL). Structural analyses of the compounds suggest that the growth inhibitory capacities of such products are

strictly linked to the presence of the bicyclic structure and to a functionalization in positions 2 and 6 different of the methyl group. The presence of *i*-Bu groups in these positions and a chlorine atom replacing the terminal hydroxy group, as it is observed in compound **7a-Cl**, increased the activity (MIC_{50} 3 μg/mL). Furthermore, the presence of a butyl group at the position 2 and/or 6 (**5c** and **5ad**) broadens the activity to genus *Staphylococcus.*

Table 6. Antimicrobial Activity (MIC_{50}, μg/mL) of Selected Compounds against the Susceptible Gram-positive Bacteria[a]

Compound	*S. epidermidis* ATCC 14990	*S. aureus* MRSA ULL	*B. subtilis* ATCC6051
5c	28	28	25
5n	>40	>40	11
5z	>40	>40	40
5ad	28	28	18
7a-Cl	>40	>40	3

[a]All assays were carried out in triplicate. All the compounds assayed were inactive (MIC_{50} > 40μg/mL) against Gram positive (*B. cereus and S. aureus*) and Gram negative (*E. coli*, *P. aeruginosa* and *P. mirabilis*) bacteria and the yeast *C. albicans* CECT 1039.

CONCLUSIONS

The EAP protocol has emerged as an efficient tool for the transformation of β,γ-unsaturated *N*-acyl oxazolidin-2-ones into 2,3,4,5,6-pentasubstituted THPs. These oxacycles were obtained in an unprecedented bicyclic form due to the rearrangement suffered in the reaction medium by the auxiliary bore by the starting material. Two

variants of the EAP protocol have been developed: a two-steps sequence and a simpler one-pot variant, showing both of them high tolerance to various functional groups and allowing the introduction of aromatic and aliphatic moieties at the positions 2, 5 and 6 of the THPs. The one-pot version permitted the introduction of five adjacent stereocenters with diastereoisomeric ratios generally greater than 95:5, as well as the generation of three C-O and two C-C bonds with average yields up to 90%. The two-steps strategy allowed the obtaining of both racemic as chiral THPs, and the modulation of the stereochemistry owned by the starting unsaturated aldol allowed the fine-tuning of the stereochemical pattern shown in the final THP, enabling thus the access to different cores of several natural products. Computational studies were coherent with those stereochemical essays and with the observed rearrangement of the oxazolidin-2-one motif. It was also revealed that the presence of the oxazolidin-2-one ring in the starting materials was absolutely necessary in order to guarantee, on the one hand, the diastereoselectivity of the process and, on the other hand, to deactivate the competing 2-oxonia-Cope rearrangement usually concomitant to the Prins cyclization. The meticulous screening of the reaction conditions led us to establish as optimal the employment of DCM as solvent and 2.5 equiv of $BF_3 \cdot OEt_2$ as promoter, although its combination with TMSCl permitted the direct synthesis of chlorinated derivatives. Other Lewis acids such as $FeBr_3$, TMSBr or TMSI were also able to yield halogenated bicycles or even 4-halo-2,3,4,5,6-pentasubstituted THPs, albeit these reaction conditions have not been optimized yet. Direct halogenation of the bicyclic THPs was also achieved, and it was found that these compounds constitute a versatile platform to access to a considerable diversity of simpler non-bicyclic THPs bearing amines, amides, carbamates, carboxylic acids and hydroxy groups. Bioassays showed that some of the synthesized THPs were active against Gram-positive bacteria, obtaining the best values

of the MIC_{50} for *Bacillus subtilis*. We expect that this complete study detailed herein will lay the foundation to explode the synthetic application of the EAP protocol.

EXPERIMENTAL SECTION

General Experimental Methods. Atoms of all the compounds were numbered according to the IUPAC name. All reagents were commercially available and used as received without further purification, unless noted otherwise. A 3.3 M solution of acetaldehyde in DCM was prepared by diluting 23 mL of commercial and volatile acetaldehyde in 100 mL of dry DCM; the molarity of the solution was checked by ^{1}H-NMR spectroscopy; the solution was stored at 2-8 ºC under Ar, being stable for at least 12 months. $BF_3{\cdot}OEt_2$ (bp = 129 ºC) was distilled and stored at –18 ºC under Ar. All solvents were dried and distilled under Ar immediately prior to use, or stored appropriately; THF was refluxed over sodium and benzophenone; DCM was distilled from CaH_2. Reactions were monitored by thin-layer chromatography (TLC) analysis employing UV light (365 nm), a phosphomolybdic acid solution 10 wt.% in methanol or a vanillin solution (6 g of vanillin, 450 mL of ethanol, 40 mL of AcOH and 30 mL of H_2SO_4); TLC was run on silica gel 60 F_{254} aluminium sheets. Flash chromatography was performed with silica gel (230–400 mesh) as the stationary phase and mixtures of *n*-hexane and EtOAc, in different proportions given in each case, as the mobile phase. Melting points were determined on a Büchi B-540 model. Optical rotations were determined on a PerkinElmer 343 polarimeter using a sodium lamp operating at 589 nm. ^{1}H-NMR (400, 500 or 600 MHz) and ^{13}C-NMR (100, 125 or 150 MHz) spectra were recorded at room temperature; chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (J) are quoted in Hertz (Hz); ^{1}H-NMR spectra are referenced to the resonance from residual $CHCl_3$ at 7.26 ppm; multiplicity is expressed by the abbreviations m (multiplet), br (broad signal), s (singlet), d (doublet), t (triplet), q

(quartet), and combinations thereof for more highly coupled system; ^{13}C-NMR spectra are referenced to the central peak of the signal from $CDCl_3$ at 77.16 ppm; multiplicity was assigned from DEPT135 and DEPT90 experiments and is expressed by the abbreviations s (C), d (CH), t (CH_2) and q (CH_3); structure elucidation was made according to literature precedents or using 2D NMR techniques such as COSY, HSQC, edited HSQC and/or HMBC; spatial elucidation was performed via NMR according to the GOESY technique. Mass spectra were recorded by using electronic impact (EI-TOF 70 eV) or by using electrospray ionization (ESI^+-TOF), as specified in each case.

Antimicrobial assay. The strains used for determining antimicrobial activity included *Staphylococcus aureus* ATCC 6538, *S. aureus* Methicillin-resistant (MRSA ULL1, clinical isolate, University of La Laguna), *S. epidermidis* ATCC 14990, *Bacillus subtillis* ATCC 6051, *B. cereus* ATCC 21772, *Escherichia coli* ATCC 9637, *Proteus mirabilis* CECT 170 (from the Colección Española de Cultivos Tipo), *Pseudomonas aeruginosa* AK958 (from the University of British Columbia, Department of Microbiology collection) and *Candida albicans* CECT1032. The MIC_{50} was determined for each compound in triplicate, by the microdilution method (range 0.08 to 40 μg/mL) in 96-well microtitre plates.[74] Wells with the same proportion of DMSO were used as controls, and never exceeded 1% (v/v). The starting microorganism density was approximately 1×10^5 to 5×10^5 colony forming units (CFU/ml), and growth was monitored by measuring the increase in the optical density at 550 nm with a microplate reader (Tecan Group Ltd., Mannedorf, Switzerland). All wells with no visible growth were subcultured by transferring in duplicate (100 μL) to agar plates. After overnight incubation, colony counts were performed and the MIC_{50} was defined as the lowest concentration of compound affecting a reduction in growth (50%) at the end of the incubation period relative to untreated controls.

General procedure for the synthesis of the β,γ-unsaturated carboxylic acids 4. A mixture of the aldehyde, malonic acid (1.1 equiv) and NMM (1.1 equiv), prepared under Ar, was heated at 95 ºC until the reaction was complete (2-8 h approx). After that, the mixture was cooled to 0 ºC, treated with a 2 M aqueous solution of H_2SO_4 (1.1 equiv) and extracted three times with DCM. The combined organic layers were washed with water, dried over anhydrous $MgSO_4$, filtered, concentrated and purified by flash chromatography to yield acids **4**.[75] Acids **4a-c** are commercially available and they were used as received without further purification. Acids **4d-f** were described in our previous publication,[30] and they were stable for at least 12 months stored under Ar at –18 ºC.

General procedure for the synthesis of the *N*-acyl oxazolidin-2-ones 3. All the subsequent operations were carried out under an Ar atmosphere. To a solution of the carboxylic acid in dry THF (0.16 M) was added, at 0 ºC, TEA (1.1 equiv). After 5 min, pivaloyl chloride (1.3 equiv) was added at 0 ºC too, obtaining a suspension of the mixed acid anhydride that was stirred 1 h at rt. Meanwhile, in another flask, a solution of the oxazolidin-2-one (1.3 equiv) in dry THF (0.3 M) was cooled to –78 ºC, treated dropwise with a 2.5 M solution of *n*-butyllithium in hexanes (1.2 equiv) and kept at that temperature until it was poured (a slow addition is not required) into the –78 ºC cooled suspension of the anhydride. After that, the mixture was allowed to warm to rt, and after 15 h it was stopped with a saturated NH_4Cl aqueous solution. Then, it was extracted three times with EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, concentrated and purified by flash chromatography to yield the desired compound **3**. The *N*-acyl oxazolidin-2-ones is usually slightly more apolar than the starting carboxylic acid. Compounds with the structure of **3** are stable for six months if they are properly stored under Ar at –18 ºC, although they begin to decompose after that time. *N*-acyl oxazolidin-2-ones **3a-f** were described in our previous publication.[30]

*(R,E)-4-Benzyl-3-(hex-3-enoyl)oxazolidin-2-one (**3g**)*. Acid **4a** (1 mL, 8.18 mmol) was submitted to the general procedure for the synthesis of the *N*-acyl oxazolidin-2-ones **3**. Purification by flash chromatography (11 cm of height of silica gel, *n*-hexane/EtOAc 75/25) provided title compound together with rests of pivaloyl chloride. To remove that contaminant, the mixture was solved in Et_2O (30 mL) and washed with H_2O (10x30 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated to yield product **3g** (2.00 g, 90%) as a yellowish oil. R_F: 0.44 (*n*-hexane/EtOAc 70/30), 0.85 (*n*-hexane/EtOAc 20/80); $[\alpha]^{25}_D$ –64.7 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 1.02 (t, *J* = 7.5 Hz, 3H, $H_{6'}$), 2.06-2.13 (m, 2H, $H_{5'}$), 2.78 (dd, *J* = 13.5, 9.8 Hz, 1H, 1xPh$\underline{CH_2}C_4$), 3.30 (dd, *J* = 13.4, 3.2 Hz, 1H, 1xPhC$\underline{H_2}C_4$), 3.61-3.73 (m, 2H, $H_{2'}$), 4.16-4.23 (m, 2H, H_5), 4.67 (ddt, *J* = 9.6, 7.5, 3.2 Hz, 1H, H_4), 5.61 (dtt, *J* = 15.6, 6.6, 1.3 Hz, 1H, $H_{3'}$), 5.70 (dtt, *J* = 15.6, 6.1, 1.3 Hz, 1H, $H_{4'}$), 7.19-7.22 (m, 2H), 7.27-7.30 (m, 1H), 7.31-7.35 (m, 2H); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 13.6 (q, $C_{6'}$), 25.8 (t, $C_{5'}$), 38.0 (t, $C_{2'}$ or Ph$\underline{C}H_2C_4$), 39.3 (t, $C_{2'}$ or Ph$\underline{C}H_2C_4$), 55.4 (d, C_4), 66.4 (t, C_5), 120.1 (d, $C_{3'}$), 127.5 (d, Ph), 129.1 (d, 2C, Ph), 129.6 (d, 2C, Ph), 135.4 (s, Ph), 137.3 (d, $C_{4'}$), 153.5 (s, C_2), 172.1 (s, $C_{1'}$); MS (EI) m/z (relative intensity): 273 $(M)^+$ (55), 178 (28), 97 (M – oxazolidin-2-one)$^+$ (55), 96 (100); HRMS: calcd for $C_{16}H_{19}NO_3$ [$(M)^+$] 273.1365, found 273.1362.

*(S,E)-3-(Hex-3-enoyl)-4-isopropyloxazolidin-2-one (**3h**)*. Acid **4a** (0.5 mL, 4.09 mmol) and (*S*)-4-isopropyloxazolidin-2-one (641 mg, 4.91 mmol, 1.2 equiv) were submitted to the general procedure for the synthesis of the *N*-acyl oxazolidin-2-ones **3** and yielded, after purification by flash chromatography (32 cm of height of silica gel, *n*-hexane/EtOAc 95/5), compound **3h** (765 mg, 83%) as a thick colorless oil. R_F: 0.32 (*n*-hexane/EtOAc 80/20), 0.55 (*n*-hexane/EtOAc 80/20 three times); $[\alpha]^{25}_D$ +75.1 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.86 (dd, *J* = 6.8, 0.9 Hz, 3H, $(C\underline{H_3})_2CHC_4$),

0.90 (dd, J = 7.0, 1.2 Hz, 3H, 1x($C\underline{H}_3$)$_2$CHC$_4$), 0.98 (td, J = 7.6, 1.2 Hz, 3H, H$_{6'}$), 2.02-2.09 (m, 2H, H$_{5'}$), 2.34-2.41 (m, 1H, (CH$_3$)$_2$C$\underline{H}$C$_4$), 3.59 (dd, J = 16.7, 6.6 Hz, 1H, H$_{2'}$), 3.70 (dd, J = 17.0, 6.7 Hz, 1H, H$_{2'}$), 4.20 (ddd, J = 9.1, 3.0, 0.9 Hz, 1H, H$_5$), 4.25-4.28 (m, 1H, H$_5$), 4.40-4.44 (m, 1H, H$_4$), 5.53-5.60 (m, 1H, H$_{3'}$), 5.63-5.70 (m, 1H, H$_{4'}$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 13.6 (q, C$_{6'}$), 14.8 (q, ($\underline{C}$H$_3$)$_2$CHC$_4$), 18.1 (q, ($\underline{C}$H$_3$)$_2$CHC$_4$), 25.7 (t, C$_{5'}$), 28.5 (d, (CH$_3$)$_2\underline{C}$HC$_4$), 39.3 (t, C$_{2'}$), 58.6 (d, C$_4$), 63.5 (t, C$_5$), 120.3 (d, C$_{3'}$), 137.1 (d, C$_{4'}$), 154.1 (s, C$_2$), 172.0 (s, C$_{1'}$); MS (EI) m/z (relative intensity): 225 $(M)^+$ (19), 210 $(M - Me)^+$ (1), 130 (42), 96 $(M - H - \text{oxazolidin-2-one})^+$ (100); HRMS: calcd for $C_{12}H_{19}NO_3$ [$(M)^+$] 225.1365, found 225.1376.

*(4R,5S)-3-((E)-Hex-3-enoyl)-4-methyl-5-phenyloxazolidin-2-one (**3i**)*. Acid **4a** (0.3 mL, 2.46 mmol) and (4*R*,5*S*)-4-methyl-5-phenyloxazolidin-2-one (523 mg, 2.95 mmol, 1.2 equiv) were submitted to the general procedure for the synthesis of the *N*-acyl oxazolidin-2-ones **3** and yielded, after purification by flash chromatography (32 cm of height of silica gel, *n*-hexane/EtOAc 90/10), compound **3i** (581 mg, 87%) as a colorless oil. R_F: 0.19 (*n*-hexane/EtOAc 80/20), 0.62 (*n*-hexane/EtOAc 60/40); $[\alpha]^{25}_D$ +29.8 (*c* 1.1, $CHCl_3$); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.89 (d, J = 6.7 Hz, 3H, C$\underline{H}_3$C$_4$), 1.00 (t, J = 7.4 Hz, 3H, H$_{6'}$), 2.04-2.10 (m, 2H, H$_{5'}$), 3.63-3.71 (m, 2H, H$_{2'}$), 4.75 (dq, J = 6.7, 6.7 Hz, 1H, H$_4$), 5.57-5.61 (m, 1H, H$_5$), 5.65-5.70 (m, 2H, H$_{3'}$, H$_{4'}$), 7.29-7.30 (m, 2H, Ph), 7.35-7.38 (m, 1H, Ph), 7.40-7.42 (m, 2H, Ph); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 13.6 (q, C$_{6'}$), 14.7 (q, $\underline{C}$H$_3$C$_4$), 25.7 (t, C$_{5'}$), 39.4 (t, C$_{2'}$), 54.9 (d, C$_4$), 79.1 (d, C$_5$), 120.1 (d, C$_{3'}$), 125.8 (d, 2C, Ph), 128.8 (d, 2C, Ph), 128.9 (d, Ph), 133.4 (s, Ph), 137.1 (d, C$_{4'}$), 153.1 (s, C$_2$), 171.8 (s, C$_{1'}$); HRMS: calcd for $C_{16}H_{19}NO_3Na$ [$(M + Na)^+$] 296.1263, found 296.1261.

General procedure for the synthesis of the *syn*-aldols 2. All the subsequent operations were carried out under an Ar atmosphere. A solution of the *N*-acyl

oxazolidin-2-ones in dry DCM (1 M) was cooled to –78 ºC. TEA (1.3 equiv) and a 1 M solution of *n*-Bu_2BOTf in DCM (1.2 equiv) were dropped sequentially, and then the mixture was stirred at that temperature for 30 min. After that, it was warmed to 0 ºC, and after 20 min it was re-cooled to –78 ºC, the aldehyde R^2CHO (1.5 equiv) was added and the mixture was allowed to warm to rt. After 15 h, the mixture was cooled to 0 ºC and it was applied an oxidative work-up: it was sequentially added a pH = 7 buffer solution (1.1 mL/mmol of *N*-acyl oxazolidin-2-ones), MeOH (2.6 mL/mmol of *N*-acyl oxazolidin-2-ones) and a 35 wt. % solution of H_2O_2 in water (1.1 mL/mmol of *N*-acyl oxazolidin-2-ones). The layers were then separated and the aqueous layer was extracted three times with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. A non-aqueous simplified work-up is also valid: a small amount of silica gel 60 (35-70 mesh) was added, the solvent was removed in the rotavap and the silica-supported crude was purified. The crude was purified by flash chromatography (the homoallylic alcohol is usually slightly more polar than the starting *N*-acyl oxazolidin-2-ones) to yield desired compounds. Stored under Ar at –18 ºC, aldols were stable for at least 12 months. Except *anti*-aldol **2a**, all the *syn*-aldols **2** were prepared as described above. *anti*-Aldol **2a** and *syn*-aldols **2a**-**g** were described in our previous publication.[30]

3-((R,E)-2-((R*)-(4-Bromophenyl)(hydroxy)methyl)hex-3-enoyl)oxazolidin-2-one (**2h**)*. *N*-acyl oxazolidin-2-one **3a** (994 mg, 5.43 mmol) was submitted to the general procedure for the synthesis of the *syn*-aldols **2** and yielded, after purification by flash chromatography (17 cm of height of silica gel, *n*-hexane/EtOAc 70/30), compound **2h** (1.18 g, 59%) as a white solid. R_F: 0.41 (*n*-hexane/EtOAc 60/40 two times); mp 60-64 ºC (from DCM/*n*-hexane); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.94 (t, J = 7.5 Hz, 3H, $H_{6'}$), 2.00-2.06 (m, 2H, $H_{5'}$), 3.09 (br s, 1H, OH), 3.85-3.91 (m, 1H, H_4), 3.93-3.99

(m, 1H, H_4), 4.26-4.31 (m, 1H, H_5), 4.32-4.39 (m, 1H, H_5), 4.74 (dd, J = 9.1, 5.7 Hz, 1H, $H_{2'}$), 4.99 (d, J = 5.7 Hz, 1H, $H_{1''}$), 5.52 (dd, J = 15.5, 9.1 Hz, 1H, $H_{3'}$), 5.69 (dt, J = 15.5, 6.1 Hz, 1H, $H_{4'}$), 7.24 (d, J = 8.5 Hz, 2H, Ar), 7.44 (d, J = 8.5 Hz, 2H, Ar); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 13.4 (q, $C_{6'}$), 25.9 (t, $C_{5'}$), 42.7 (t, C_4), 53.8 (d, $C_{2'}$), 62.0 (t, C_5), 73.9 (d, $C_{1''}$), 121.3 (d, $C_{3'}$), 121.7 (s, Ar), 128.7 (d, 2C, Ar), 131.3 (d, 2C, Ar), 139.8 (s, Ar), 140.7 (d, $C_{4'}$), 153.0 (s, C_2), 173.7 (s, $C_{1'}$); HRMS: calcd for $C_{16}H_{18}{}^{79}BrNO_4Na$ [$(M + Na)^+$] 390.0317, found 390.0314.

(R)-4-Benzyl-3-((R,E)-2-((S)-1-hydroxyethyl)hex-3-enoyl)oxazolidin-2-one ***(2i)***. *N*-acyl oxazolidin-2-one **3g** (643 mg, 2.35 mmol) was submitted to the general procedure for the synthesis of the *syn*-aldols **2** and yielded, after purification by flash chromatography (18 cm of height of silica gel, *n*-hexane/EtOAc 70/30), compound **2i** (559 mg, 75%) as a colorless oil. R_F: 0.42 (*n*-hexane/EtOAc 60/40); $[\alpha]^{25}_D$ 0 (*c* 1.0, $CHCl_3$), -22.0 (*c* 1.7, Et_2O); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 1.04 (t, J = 7.5 Hz, 3H, $H_{6'}$), 1.19 (d, J = 6.4 Hz, 3H, $H_{2''}$), 2.11-2.17 (m, 2H, $H_{5'}$), 2.79 (dd, J = 13.4, 9.2 Hz, 1H, C$\underline{H}_2$Ph), 2.99 (br s, 1H, OH), 3.19 (dd, J = 13.5, 2.9 Hz, 1H, C$\underline{H}_2$Ph), 4.13-4.19 (m, 2H, 1xH_5, $H_{1''}$), 4.20-4.25 (m, 1H, 1xH_5), 4.44 (dd, J = 9.2, 3.9 Hz, 1H, $H_{2'}$), 4.70-4.76 (m, 1H, H_4), 5.60 (dd, J = 15.3, 9.3 Hz, 1H, $H_{3'}$), 5.90 (dt, J = 15.4, 6.9 Hz, 1H, $H_{4'}$), 7.17-7.21 (m, 2H, Ph), 7.27-7.29 (m, 1H, Ph), 7.30-7.34 (m, 2H, Ph); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 13.7 (q, $C_{6'}$), 20.0 (q, $C_{2''}$), 26.0 (t, $C_{5'}$), 37.7 (t, $\underline{C}H_2$Ph), 52.5 (d, $C_{2'}$), 55.1 (d, C_4), 66.0 (t, C_5), 68.2 (d, $C_{1''}$), 121.6 (d, $C_{3'}$), 127.6 (d, Ph), 129.1 (d, 2C, Ph), 129.6 (d, 2C, Ph), 135.1 (s, Ph), 140.2 (d, $C_{4'}$), 153.1 (s, C_2), 174.8 (s, $C_{1'}$); HRMS: calcd for $C_{18}H_{23}NO_4Na$ [$(M + Na)^+$] 340.1525, found 340.1520.

(R)-4-Benzyl-3-((R,E)-2-((S)-1-hydroxy-3-phenylpropyl)hex-3-enoyl)oxazolidin-2-one ***(2j)***. *N*-acyl oxazolidine-2-one **3g** (600 mg, 2.19 mmol) was submitted to the general procedure for the synthesis of the *syn*-aldols **2** and yielded, after purification by flash

chromatography (30 cm of height of silica gel, *n*-hexane/EtOAc 80/20), compound **2j** (533 mg, 60%) as a yellow oil. R_F: 0.39 (*n*-hexane/EtOAc 70/30); $[\alpha]^{25}_D$ –13.2 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 1.03 (t, *J* = 7.5 Hz, 3H, $H_{6'}$), 1.63 (br s, 1H, OH), 1.68-1.75 (m, 1H, $H_{2''}$), 1.82-1.90 (m, 1H, $H_{2''}$), 2.10-2.16 (m, 2H, $H_{5'}$), 2.66-2.72 (m, 1H, $H_{3''}$), 2.78 (d, *J* = 13.5, 9.0 Hz, 1H, $C_4C\underline{H}_2Ph$), 2.81-2.87 (m, 1H, $H_{3''}$), 3.20 (dd, *J* = 13.5, 3.5 Hz, 1H, $C_4C\underline{H}_2Ph$), 3.97 (dt, *J* = 9.1, 3.6 Hz, 1H, $H_{1''}$), 4.14-4.22 (m, 2H, H_5), 4.50 (dd, *J* = 9.3, 3.9 Hz, 1H, $H_{2'}$), 4.68-4.73 (m, 1H, H_4), 5.61 (ddt, *J* = 15.4, 9.2, 1.4 Hz, 1H, $H_{3'}$), 5.92 (dt, *J* = 15.4, 6.4 Hz, 1H, $H_{4'}$), 7.17-7.22 (m, 5H, Ph), 7.27-7.34 (m, 5H, Ph); ^{13}C-NMR (150MHz, δ, $CDCl_3$): 13.7 (q, $C_{6'}$), 26.1 (t, $C_{5'}$), 32.0 (t, $C_{3''}$), 35.8 (t, $C_{2''}$), 37.7 (t, $C_4\underline{C}H_2Ph$), 51.2 (d, $C_{2'}$), 55.1 (d, C_4), 66.0 (t, C_5), 71.1 (d, $C_{1''}$), 121.3 (d, $C_{3'}$), 125.9 (d, Ph), 127.6 (d, Ph), 128.5 (d, 2C, Ph), 128.7 (d, 2C, Ph), 129.1 (d, 2C, Ph), 129.6 (d, 2C, Ph), 135.1 (s, Ph), 140.3 (d, $C_{4'}$), 142.1 (s, Ph), 153.0 (s, C_2), 175.0 (s, $C_{1'}$); HRMS: calcd for $C_{25}H_{29}NO_4Na$ $[(M + Na)^+]$ 430.1994, found 430.1998.

(S)-3-((S,E)-2-((R)-1-Hydroxyethyl)hex-3-enoyl)-4-isopropyloxazolidin-2-one ***(2k)***. *N*-acyl oxazolidin-2-one **3h** (276 mg, 1.23 mmol) was submitted to the general procedure for the synthesis of the *syn*-aldols **2** and yielded, after purification by flash chromatography (25 cm of height of silica gel, *n*-hexane/EtOAc 70/30), compound **2k** (283 mg, 86%) as a thick colorless oil. R_F: 0.21 (*n*-hexane/EtOAc 70/30); $[\alpha]^{25}_D$ –27.8 (*c* 1.1, $CHCl_3$); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.81 (d, *J* = 6.9 Hz, 3H, $(C\underline{H}_3)_2CHC_4$), 0.88 (d, *J* = 6.9 Hz, 3H, $(C\underline{H}_3)_2CHC_4$), 0.96 (t, *J* = 7.5 Hz, 3H, $H_{6'}$), 1.14 (d, *J* = 6.4 Hz, 3H, $H_{2''}$), 2.03-2.08 (m, 2H, $H_{5'}$), 2.25-2.34 (m, 1H, $(CH_3)_2C\underline{H}C_4$), 3.10 (br s, 1H, OH), 4.09-4.14 (m, 1H, $H_{1''}$), 4.17 (dd, *J* = 9.1, 3.3 Hz, 1H, H_5), 4.25 (dd, *J* = 8.9, 8.9 Hz, 1H, H_5), 4.43-4.48 (m, 2H, H_4, $H_{2'}$), 5.52 (ddq, *J* = 15.6, 9.2, 1.3 Hz, 1H, $H_{3'}$), 5.87 (dt, *J* = 15.0, 6.5 Hz, 1H, $H_{4'}$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 13.6 (q, $C_{6'}$), 14.6 (q,

($\underline{C}H_3)_2CHC_4$), 17.9 (q, ($\underline{C}H_3)_2CHC_4$), 19.9 (q, $C_{2''}$), 25.9 (t, $C_{5'}$), 28.3 (d, $(CH_3)_2\underline{C}HC_4$), 52.2 (d, $C_{2'}$), 58.2 (d, C_4), 63.2 (t, C_5), 67.8 (d, $C_{1''}$), 121.7 (d, $C_{3'}$), 140.1 (d, $C_{4'}$), 153.6 (s, C_2), 175.1 (s, $C_{1'}$); MS (EI) m/z (relative intensity): 225 (M – H – *i*-Pr)$^+$ (1), 141 (M – oxazolidin-2-one)$^+$ (1), 128 (oxazolidin-2-one)$^+$ (100), 113 (M – *N*-acyloxazolidin-2-one)$^+$ (38); HRMS: calcd for $C_{11}H_{15}NO_4$ [(M – H – *i*-Pr)$^+$] 225.1001, found 225.1007.

*(S)-3-((S,E)-2-((R)-1-Hydroxy-3-phenylpropyl)hex-3-enoyl)-4-isopropyloxazolidin-2-one (**2l**)*. *N*-acyl oxazolidin-2-one **3h** (194 mg, 0.86 mmol) was submitted to the general procedure for the synthesis of the *syn*-aldols **2** and yielded, after purification by flash chromatography (25 cm of height of silica gel, *n*-hexane/EtOAc 80/20), compound **2l** (215 mg, 69%) as an amorphous white solid. R_F: 0.33 (*n*-hexane/EtOAc 70/30); $[\alpha]^{25}_D$ – 23.8 (*c* 1.1, $CHCl_3$); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.80 (d, *J* = 7.0 Hz, 3H, ($C\underline{H}_3)_2CHC_4$), 0.87 (d, *J* = 7.0 Hz, 3H, ($C\underline{H}_3)_2CHC_4$), 0.95 (t, *J* = 7.5 Hz, 3H, $H_{6'}$), 1.63-1.70 (m, 1H, $H_{2''}$), 1.78-1.86 (m, 1H, $H_{2''}$), 2.02-2.08 (m, 2H, $H_{5'}$), 2.25-2.34 (m, 1H, $(CH_3)_2C\underline{H}C_4$), 2.63-2.69 (m, 1H, $H_{3''}$), 2.77-2.83 (m, 1H, $H_{3''}$), 3.21 (br s, 1H, OH), 3.91-3.95 (m, 1H, $H_{1''}$), 4.16 (dd, *J* = 9.2, 3.2 Hz, 1H, H_5), 4.23 (dd, *J* = 8.7, 8.7 Hz, 1H, H_5), 4.43 (dt, *J* = 8.3, 3.4 Hz, 1H, H_4), 4.52 (dd, *J* = 9.2, 3.4 Hz, 1H, $H_{2'}$), 5.54 (ddt, *J* = 15.6, 9.2, 1.5 Hz, 1H, $H_{3'}$), 5.88 (dt, *J* = 15.4, 6.5 Hz, 1H, $H_{4'}$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 13.7 (q, $C_{6'}$), 14.7 (q, ($\underline{C}H_3)_2CHC_4$), 18.0 (q, ($\underline{C}H_3)_2CHC_4$), 26.0 (t, $C_{5'}$), 28.3 (d, $(CH_3)_2\underline{C}HC_4$), 32.0 (t, $C_{3''}$), 35.8 (t, $C_{2''}$), 50.9 (d, $C_{2'}$), 58.2 (d, C_4), 63.2 (t, C_5), 70.7 (d, $C_{1''}$), 121.5 (d, $C_{3'}$), 125.9 (d, Ph), 128.5 (d, 2C, Ph), 128.7 (d, 2C, Ph), 140.2 (d, $C_{4'}$), 142.1 (s, Ph), 153.5 (s, C_2), 175.4 (s, $C_{1'}$); MS (EI) m/z (relative intensity): 359 (M)$^+$ (1), 316 (M – *i*-Pr)$^+$ (1), 225 (M + 1 – Me – Ph – *i*-Pr)$^+$ (47), 128 (oxazolidin-2-one)$^+$ (128); HRMS: calcd for $C_{21}H_{29}NO_4$ [(M)$^+$] 359.2097, found 359.2111.

*(4R,5S)-3-((2R,3S)-2-((E)-But-1-en-1-yl)-3-hydroxyheptanoyl)-4-methyl-5-phenyloxazolidin-2-one (**2m**)*. *N*-acyl oxazolidin-2-one **3i** (207 mg, 0.76 mmol) was submitted to the general procedure for the synthesis of the *syn*-aldols **2** and yielded, after purification by flash chromatography (21 cm of height of silica gel, *n*-hexane/EtOAc 85/15), compound **2m** (175 mg, 64%) as a thick colorless oil. R_F: 0.33 (*n*-hexane/EtOAc 80/20); $[\alpha]^{25}_D$ +75.3 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.84-0.88 (br m, 3H, C$\underline{H}_3$C$_4$), 0.89-0.94 (br m, 3H, H$_{5''}$), 0.97-1.03 (br m, 3H, H$_{6'}$), 1.29-1.39 (br m, 3H, 3xC$_{1''}$(C$\underline{H}_2$)$_3$CH$_3$), 1.42-1.55 (br m, 3H, 3xC$_{1''}$(C$\underline{H}_2$)$_3$CH$_3$), 2.03-2.13 (br m, 2H, H$_{5'}$), 3.01 (br s, 1H, OH), 3.96 (br m, 1H, H$_{1''}$), 4.45-4.51 (br m, 1H, H$_{2'}$), 4.77-4.85 (br m, 1H, H$_4$), 5.53-5.61 (br m, 1H, H$_{3'}$), 5.65-5.69 (br m, 1H, H$_5$), 5.82-5.89 (br m, 1H, H$_{4'}$), 7.27-7.32 (m, 2H, Ph), 7.35-7.44 (m, 3H, Ph); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 13.7 (q, C$_{6'}$), 14.1 (q, C$_{5''}$), 14.4 (q, $\underline{C}$H$_3$C$_4$), 22.7 (t, C$_{4''}$), 26.0 (t, C$_{5'}$), 28.0 (t, C$_{3''}$), 33.9 (t, C$_{2''}$), 51.3 (d, C$_{2'}$), 54.8 (d, C$_4$), 72.0 (d, C$_{1''}$), 78.9 (d, C$_5$), 121.4 (d, C$_{3'}$), 125.8 (d, 2C, Ph), 128.9 (d, 2C, Ph), 129.0 (d, Ph), 133.4 (s, Ph), 139.6 (d, C$_{4'}$), 152.7 (s, C$_2$), 174.9 (s, C$_{1'}$); HRMS: calcd for $C_{21}H_{29}NO_4Na$ [$(M + Na)^+$] 382.1994, found 382.1995.

General procedure for the synthesis of the bicycles 5. Starting from aldols **2** (two-steps EAP): to a solution of the homoallylic alcohol and the aldehyde R^3CHO (1.5 equiv) in dry DCM (0.1 M) was added, under Ar atmosphere, $BF_3{\cdot}OEt_2$ (2.5 equiv). Once TLC analysis showed full conversion (less than 30 min), the mixture was quenched with H_2O. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated.[76] The crude was purified by flash chromatography (the bicycle is usually slightly more apolar than the starting homoallylic alcohol) to yield the desired product. Starting from *N*-acyl oxazolidin-2-ones **3** (one-pot EAP): a

solution of the *N*-acyl oxazolidin-2-one in dry DCM (1 M) was cooled to –78 ºC. TEA (1.3 equiv) and a 1 M solution of *n*-Bu_2BOTf in DCM (1.2 equiv) were dropped under an Ar atmosphere sequentially and the mixture was stirred at that temperature for 30 min. Then, it was warmed to 0 ºC, and after 20 min it was re-cooled to –78 ºC, the aldehyde R^2CHO (1 equiv) was added and the mixture was allowed to warm to rt. After 15 h, the aldehyde R^3CHO (1.5 equiv) and $BF_3{\cdot}OEt_2$ (2.5 equiv) were sequentially added under an Ar atmosphere. Once TLC analysis revealed full conversion (less than 30 min), the mixture was quenched and purified as described above. Traces of an UV-visible polar by-product, the 2-oxonia-Cope rearranged isomer **6**, could be punctually detected. Bicycles **5** are highly stable, and they can be stored without an Ar atmosphere at rt without decomposition. Except products **5c-Ac**, **5l**, **5r**, **5u**, **5ag**, **5ah** and **5ai** the rest of bicycles **5** were described in our previous publication (see Supporting Information for the correlation of the molecules numbering between both publications).[30]

*2-((4aS,5S,7R,8R,8aS)-5,7-Dibutyl-8-ethyl-2,4-dioxotetrahydro-2H,5H-pyrano[3,4-e][1,3]oxazin-3(4H)-yl)ethyl acetate (**5c-Ac**)*. Aldol **2c** (38.7 mg, 0.14 mmol) was submitted to the general procedure for the synthesis of the bicycles **5** (two-steps EAP) using acetic acid (1.4 mL, 0.1M) as solvent to yield, after purification by flash chromatography (20 cm of height of silica gel, *n*-hexane/EtOAc 80/20), title compound **5c-Ac** (41 mg, 71%, >95:5 dr) as an amorphous white solid. R_F: 0.4 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.87-0.97 (m, 9H, $H_{2'''}$, $H_{4'}$, $H_{4''}$), 1.26-1.79 (m, 14H, H_8, 1x$H_{1'}$, 6xCH_2), 2.01 (s, 3H, OCOC$\underline{H}_3$), 2.28 (br s, 1H, $H_{1'}$), 2.38 (dd, *J* = 11.1, 11.1 Hz, 1H, H_{4a}), 3.10 (dd, *J* = 8.4, 8.4 Hz, 1H, H_7), 3.41 (t, *J* = 8.7 Hz 1H, H_5), 3.92-4.00 (m, 1H, NC$\underline{H}_2CH_2OCOCH_3$), 4.07-4.13 (m, 1H, NC$\underline{H}_2CH_2OCOCH_3$), 4.17 (t, *J* = 11.1 Hz, 1H, H_{8a}), 4.27 (br s, 2H, $NCH_2C\underline{H}_2OCOCH_3$); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 9.5 (q, $C_{2'''}$), 14.2 (q, $C_{4'}$ or $C_{4''}$),

14.2 (q, $C_{4'}$ or $C_{4''}$), 18.6 (t, $C_{1'''}$), 20.91 (q, $NCH_2CH_2OCO\underline{C}H_3$), 22.6 (t, $C_{3'}$ or $C_{3''}$), 22.6 (t, $C_{2'}$ or $C_{2''}$), 27.6 (t, $C_{2'}$ or $C_{2''}$), 32.1 (t, $C_{1''}$), 34.0 (t, $C_{1'}$), 41.5 (t, $N\underline{C}H_2CH_2OCOCH_3$), 45.2 (d, C_8), 47.5 (d, C_{4a}), 61.6 (t, $NCH_2\underline{C}H_2OCOCH_3$), 74.7 (d, C_5), 76.7 (d, C_{8a}), 76.9 (d, C_7), 152.5 (s, C_2), 169.5 (s, C_4), 171.2 (s, $O\underline{C}OCH_3$); HRMS: calcd for $C_{21}H_{35}NO_6Na$ $[(M + Na)^+]$ 420.2362, found 420.2361.

(4a'S,5'S*,8'S*,8a'S*)-8'-Ethyl-3'-(2-hydroxyethyl)-5'-methyltetrahydro-2'H-spiro[cyclohexane-1,7'-pyrano[3,4-e][1,3]oxazine]-2',4'(3'H)-dione* ***(5l)***. Aldol **2b** (30 mg, 0.13 mmol) and cyclohexanone (0.03 mL, 0.29 mmol, 2.2 equiv) were submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (21 cm of height of silica gel, *n*-hexane/EtOAc 75/25), THF **8l** (7.8 mg, 19%, 80:20 dr), title compound **5l** (10 mg, 23%, >95:5 dr) and previously described bicycle **5b** (8 mg, 45%, >95:5 dr). **5l** was isolated as a colorless oil and its description is given below. R_F: 0.44 (*n*-hexane/EtOAc 60/40 two times); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 1.11 (t, J = 7.3 Hz, 3H, $H_{2'''}$), 1.11-1.17 (m, 1H, $C\underline{H}_2$ from cyclohexane), 1.21-1.26 (m, 1H, $C\underline{H}_2$ from cyclohexane), 1.31-1.39 (m, 1H, $C\underline{H}_2$ from cyclohexane), 1.41-1.50 (m, 6H, H_8, 3x$C\underline{H}_2$ from cyclohexane, 2x$H_{1'''}$), 1.52 (d, J = 6.0 Hz, 3H, $H_{1'}$), 1.65-1.70 (m, 2H, $C\underline{H}_2$ from cyclohexane), 1.71-1.77 (m, 2H, $C\underline{H}_2$ from cyclohexane), 1.97 (br s, 1H, OH), 2.34 (dd, J = 12.3, 9.9 Hz, 1H, H_{4a}), 3.74 (dq, J = 9.8, 6.0 Hz, 1H, H_5), 3.77-3.85 (br m, 2H, $NCH_2C\underline{H}_2OH$), 3.89 (ddd, J = 14.1, 6.0, 4.2 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.09 (ddd, J = 14.1, 6.0, 4.2 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.31 (dd, J = 12.1, 10.5 Hz, 1H, H_{8a}); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 15.2 (q, $C_{2'''}$), 20.4 (t, $\underline{C}H_2$ from cyclohexane), 21.3 (t, $\underline{C}H_2$ from cyclohexane), 21.4 (q, $C_{1'}$), 21.7 (t, $C_{1'''}$), 25.7 (t, $\underline{C}H_2$ from cyclohexane), 26.0 (t, $\underline{C}H_2$ from cyclohexane), 36.4 (t, $\underline{C}H_2$ from cyclohexane), 44.4 (t, $N\underline{C}H_2CH_2OH$), 50.0 (d, C_{4a}), 51.6 (d, C_8), 61.2 (t, $NCH_2\underline{C}H_2OH$),

63.4 (d, C_5), 76.8 (s, C_7), 78.3 (d, C_{8a}), 152.7 (s, C_2), 169.7 (s, C_4); HRMS: calcd for $C_{17}H_{27}NO_5Na$ [$(M + Na)^+$] 348.1787, found 348.1792.

(4aS,5S*,7S*,8S*,8aS*)-8-Ethyl-3-(2-hydroxyethyl)-7-(2-methoxyphenyl)-5-methyltetrahydro-2H,5H-pyrano[3,4-e][1,3]oxazine-2,4(3H)-dione* ***(5r)***. Aldol **2b** (54 mg, 0.24 mmol) was submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (25 cm of height of silica gel, *n*-hexane/EtOAc 70/30), THF **8r** (16 mg, 20%, 80:20 dr), title compound **5r** (17 mg, 20%, >95:5 dr) and previously described bicycle **5b** (3 mg, 10%, >95:5 dr). **5r** was isolated as a thick colorless oil and its description is given below. R_F: 0.28 (*n*-hexane/EtOAc 60/40 two times); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.73 (t, J = 7.7 Hz, 3H, $H_{2'''}$), 1.28-1.34 (m, 1H, $H_{1'''}$), 1.47-1.53 (m, 1H, $H_{1'''}$), 1.58 (d, J = 6.1 Hz, 3H, $H_{1'}$), 1.89-2.14 (m, 2H, H_8, OH), 2.56 (dd, J = 12.1, 9.6 Hz, 1H, H_{4a}), 3.77-3.86 (m, 3H, H_5, $NCH_2C\underline{H}_2OH$), 3.81 (s, 3H, MeO), 3.93 (ddd, J = 14.0, 6.8, 4.3 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.13 (ddd, J = 14.0, 5.8, 4.3 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.39 (dd, J = 11.6, 10.9 Hz, 1H, H_{8a}), 4.79 (br s, 1H, H_7), 6.88-6.89 (m, 1H, Ar), 6.99-7.02 (m, 1H, Ar), 7.27-7.30 (m, 1H, Ar), 7.37-7.41 (m, 1H, Ar); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 10.3 (q, $C_{2'''}$), 19.3 (t, $C_{1'''}$), 21.1 (q, $C_{1'}$), 44.5 (t, $N\underline{C}H_2CH_2OH$), 47.1 (d, C_8), 49.2 (d, C_{4a}), 55.6 (q, MeO), 61.1 (t, $NCH_2\underline{C}H_2OH$), 71.9 (d, C_5), 72.7 (d, C_7), 77.8 (d, C_{8a}), 110.9 (d, $C_{3''}$), 121.3 (d, $C_{5''}$), 127.6 (s, $C_{1''}$), 128.1 (d, $C_{6''}$), 129.5 (d, $C_{4''}$), 152.4 (s, C_2), 156.8 (s, $C_{2''}$), 169.4 (s, C_4); HRMS: calcd for $C_{19}H_{25}NO_6Na$ [$(M + Na)^+$] 386.1580, found 386.1589.

(4aR,5R*,7R*,8R*,8aS*)-5-(4-Bromophenyl)-8-ethyl-3-(2-hydroxyethyl)-7-methyltetrahydro-2H,5H-pyrano[3,4-e][1,3]oxazine-2,4(3H)-dione* ***(5u)***. Aldol **2h** (72 mg, 0.20 mmol) and acetaldehyde (0.09 mL of a 3.3 M solution in DCM, 0.30 mmol, 1.5 equiv) were submitted to the general procedure for the synthesis of the

bicycles **5** (two-steps EAP) and yielded, after purification by flash chromatography (25 cm of height of silica gel, *n*-hexane/EtOAc 70/30), compound **5u** (36 mg, 43%, >95:5 dr) and previously described bicycle **5b** (3 mg, 6%, >95:5 dr). Alternatively, *N*-acyl oxazolidin-2-one **3a** (320 mg, 1.75 mmol) was submitted to the general procedure for the synthesis of the bicycles **5** (one-pot EAP) and yielded, after purification by flash chromatography (25 cm of height of silica gel, *n*-hexane/EtOAc 70/30) title compound **5u** (155 mg, 22%, >95:5 dr) and a small amount of **5b** (19 mg, 5%, >95:5 dr). **5u** was isolated as a white solid and its description is given below. R_F: 0.36 (*n*-hexane/EtOAc 60/40 two times); mp 72-77 ºC (from DCM/*n*-hexane); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.98 (t, J = 7.5 Hz, 3H, $H_{2'''}$), 1.31 (d, J = 6.2 Hz, 3H, $H_{1''}$), 1.63-1.70 (m, 1H, $H_{1'''}$), 1.73-1.84 (m, 2H, H_8, $H_{1'''}$), 1.89 (br s, 1H, OH), 2.94 (dd, J = 11.9, 10.0 Hz, 1H, H_{4a}), 3.50 (dq, J = 9.7, 6.1 Hz, 1H, H_7), 3.67-3.77 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.78-3.83 (m, 1H, $NC\underline{H}_2CH_2OH$), 3.94-4.00 (m, 1H, $NC\underline{H}_2CH_2OH$), 4.38 (dd, J = 11.2, 11.2 Hz, 1H, H_{8a}), 4.47 (d, J = 10.0 Hz, 1H, H_5), 7.30 (d, J = 8.4 Hz, 2H, 2x$H_{2'}$), 7.50 (d, J = 8.4 Hz, 2H, 2x$H_{3'}$); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 9.6 (q, $C_{2'''}$), 18.9 (t, $C_{1'''}$), 19.1 (q, $C_{1''}$), 44.4 (t, $N\underline{C}H_2CH_2OH$), 46.9 (d, C_8), 48.3 (d, C_{4a}), 60.8 (t, $NCH_2\underline{C}H_2OH$), 74.9 (d, C_7), 76.4 (d, C_{8a}), 76.8 (d, C_5), 122.7 (s, $C_{4'}$), 129.7 (d, 2C, 2x$C_{2'}$), 131.6 (d, 2C, 2x$C_{3'}$), 138.5 (s, $C_{1'}$), 152.0 (s, C_2), 168.4 (s, C_4); HRMS: calcd for $C_{18}H_{22}{}^{79}BrNO_5Na$ [(^{79}M + Na)$^+$] 434.0579, found 434.0584.

(4aS,5S,7R,8R,8aS)-8-Ethyl-3-((R)-1-hydroxy-3-phenylpropan-2-yl)-5,7-dimethyltetrahydropyrano[3,4-e][1,3]oxazine-2,4(3H,7H)-dione ***(5ag)***. Aldol **2i** (26 mg, 83 μmol) and acetaldehyde (37 μL of a 3.3 M solution in DCM, 125 mmol, 1.5 equiv) were submitted to the general procedure for the synthesis of the bicycles **5** (two-steps EAP) and yielded, after purification by flash chromatography (18 cm of height of silica gel, *n*-hexane/EtOAc 70/30), 3-(*N*-acyl-oxazolidin-2-one)-THP **21a**

(3 mg, 9%, >95:5 dr) and title bicycle **5ag** (19 mg, 62%, >95:5 dr). Appearance: yellowish oil; R_F: 0.31 (*n*-hexane/EtOAc 60/40); $[\alpha]^{25}_D$ –54.5 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.80 (t, *J* = 7.5 Hz, 3H, $H_{2'''}$), 1.19 (d, *J* = 6.2 Hz, 3H, $H_{1''}$), 1.40-1.47 (m, 2H, H_8, $H_{1'''}$), 1.44 (d, *J* = 6.0 Hz, 3H, $H_{1'}$), 1.58-1.62 (m, 1H, $H_{1'''}$), 2.14 (dd, *J* = 12.1, 9.2 Hz, 1H, H_{4a}), 2.81 (br s, 1H, OH), 3.05 (dd, *J* = 13.8, 6.0 Hz, 1H, 1xC$\underline{H}_2$Ph), 3.08 (br s, 1H, H_7), 3.13 (br s, 1H, H_{8a}), 3.19 (dd, *J* = 14.0, 11.4 Hz, 1H, 1xC$\underline{H}_2$Ph), 3.26 (br s, 1H, H_5), 3.91 (dd, *J* = 11.7, 3.5 Hz, 1H, $\underline{C}H_2OH$), 4.06-4.12 (br m, 1H, C$\underline{H}_2$OH), 5.13-5.20 (br m, 1H, NC$\underline{H}$(CH_2Ph)CH_2OH), 7.16-7.19 (m, 2H, Ph), 7.19-7.22 (m, 1H, Ph), 7.25-7.29 (m, 2H, Ph); ^{1}H-NMR (600 MHz, δ, C_6D_6, T = 320 K): 0.64 (t, *J* = 7.6 Hz, 3H, $H_{2'''}$), 0.96 (d, *J* = 6.2 Hz, 3H, $H_{1''}$), 1.09-1.19 (m, 2H, H_8, $H_{1'''}$), 1.31-1.41 (m, 1H, $H_{1'''}$), 1.49 (d, *J* = 6.0 Hz, 3H, $H_{1'}$), 1.65 (dd, *J* = 12.0, 9.6 Hz, 1H, H_{4a}), 2.18 (br s, 1H, OH), 2.65 (dq, *J* = 9.8, 6.2 Hz, 1H, H_7), 2.84 (dd, *J* = 13.9, 6.1 Hz, 1H, 1xC$\underline{H}_2$Ph), 3.03-3.10 (m, 2H, H_5, H_{8a}), 3.21 (dd, *J* = 14.0, 11.2 Hz, 1H, 1xC$\underline{H}_2$Ph), 3.71 (dd, *J* = 11.4, 4.4 Hz, 1H, C$\underline{H}_2$OH), 4.06 (dd, *J* = 11.4, 7.4 Hz, 1H, C$\underline{H}_2$OH), 5.12-5.16 (br m, 1H, NC$\underline{H}$(CH_2Ph)CH_2OH), 6.97-7.00 (m, 1H, Ph), 7.06-7.09 (m, 1H, Ph), 7.11-7.13 (m, 2H, Ph); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 9.2 (q, $C_{2'''}$), 18.7 (t, $C_{1'''}$), 18.9 (q, $C_{1''}$), 20.9 (q, $C_{1'}$), 33.3 (t, $\underline{C}H_2Ph$), 46.4 (d, C_8), 48.8 (d, C_{4a}), 55.5 (d, N$\underline{C}$H(CH_2Ph)CH_2OH),[77] 63.5 (t, $\underline{C}H_2OH$), 71.0 (d, C_5), 73.6 (d, C_7), 76.2 (d, C_{8a}),[78] 126.9 (d, Ph), 128.7 (d, 2C, Ph), 129.2 (d, 2C, Ph), 137.5 (s, Ph), 151.9 (s, C_2), 169.4 (s, C_4); ^{13}C-NMR (150 MHz, δ, C_6D_6, T = 320 K): 9.7 (q, $C_{2'''}$), 19.0 (q, $C_{1''}$), 19.2 (t, $C_{1'''}$), 21.0 (q, $C_{1'}$), 33.9 (t, $\underline{C}H_2Ph$), 46.9 (d, C_8), 49.0 (d, C_{4a}), 56.4 (d, N$\underline{C}$H(CH_2Ph)CH_2OH),[79] 63.8 (t, $\underline{C}H_2OH$), 71.1 (d, C_5), 73.6 (d, C_7), 76.4 (d, C_{8a}), 126.8 (d, Ph), 128.7 (d, 2C, Ph), 129.6 (d, 2C, Ph), 138.4 (s, Ph), 151.5 (s, C_2), 169.5 (s, C_4); MS (EI) m/z (relative intensity): 361 $(M)^+$ (1), 343 $(M - H_2O)^+$ (2), 228 (M + 2 – $CH(Bn)CH_2OH)^+$ (83), 185 (10), 184 $(M - N(CO)CH(Bn)CH_2OH)^+$ (78), 91 (100);

HRMS: calcd for $C_{20}H_{27}NO_5$ [$(M)^+$] 361.1889, found 361.1884 and calcd for $C_{20}H_{27}NO_5Na$ [$(M + Na)^+$] 384.1787, found 384.1785.

*(4aR,5R,7S,8S,8aR)-8-Ethyl-3-((S)-1-hydroxy-3-methylbutan-2-yl)-5,7-dimethyltetrahydro-2H,5H-pyrano[3,4-e][1,3]oxazine-2,4(3H)-dione (**5ah**)*. Aldol **2k** (58 mg, 0.22 mmol) and acetaldehyde (0.1 mL of a 3.3 M solution in DCM, 0.33 mmol, 1.5 equiv) were submitted to the general procedure for the synthesis of the bicycles **5** (two-steps EAP) and yielded, after purification by flash chromatography (28 cm of height of silica gel, *n*-hexane/EtOAc 85/15), 3-(*N*-acyl-oxazolidin-2-one)-THP **21b** (11 mg, 16%, >95:5 dr) and title bicycle **5ah** (29 mg, 43%, 92:8 dr). Appearance: colorless oil; R_F: 0.33 (*n*-hexane/EtOAc 60/40); $[\alpha]^{25}_D$ +104.4 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.84 (d, *J* = 6.6 Hz, 3H, 1x$(C\underline{H}_3)_2CH$), 0.92 (t, *J* = 7.6 Hz, 3H, $H_{2'''}$), 1.04 (d, *J* = 6.4 Hz, 3H, 1x$(C\underline{H}_3)_2CH$), 1.27 (d, *J* = 6.1 Hz, 3H, $H_{1''}$), 1.52 (d, *J* = 6.1 Hz, 3H, $H_{1'}$), 1.55-1.63 (m, 2H, H_8, 1x$H_{1'''}$), 1.69-1.76 (m, 1H, $H_{1'''}$), 2.36 (dd, *J* = 12.2, 9.8 Hz, 1H, H_{4a}), 2.35-2.45 (m, 1H, $(CH_3)_2C\underline{H}$), 2.89 (br s, 1H, OH), 3.31 (dq, *J* = 9.7, 6.2 Hz, 1H, H_7), 3.61 (dq, *J* = 9.5, 6.0 Hz, 1H, H_5), 3.79 (dd, *J* = 12.1, 2.7 Hz, 1H, 1x$C\underline{H}_2OH$), 4.01-4.08 (m, 1H, 1x$C\underline{H}_2OH$), 4.11 (dd, *J* = 12.1, 10.4 Hz, 1H, H_{8a}), 4.34-4.40 (m, 1H, $NC\underline{H}(CH_2OH)CH(CH_3)_2$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.7 (q, $C_{2'''}$), 19.0 (t, $C_{1'''}$), 19.1 (q, $C_{1''}$), 20.0 (q, 1x$(\underline{C}H_3)_2CH$), 20.2 (q, 1x$(\underline{C}H_3)_2CH$), 21.0 (q, $C_{1'}$), 25.4 (d, $(CH_3)_2\underline{C}H$), 47.0 (d, C_8), 49.3 (d, C_{4a}), 62.3 (d, $N\underline{C}H(CH_2OH)CH(CH_3)_2$),[80] 62.7 (t, $\underline{C}H_2OH$), 71.2 (d, C_5), 73.9 (d, C_7), 76.6 (d, C_{8a}), 152.3 (s, C_2), 169.8 (s, C_4); MS (EI) m/z (relative intensity): 314 $(M + H)^+$ (2), 284 $(M - Et)^+$ or $(M - 2\ Me)^+$ (11), 283 $(M - Et - H)^+$ or $(M + 1 - CH_2OH)^+$ (66), 282 $(M - CH_2OH)^+$ (18),[81] 240 $(M + 1 - Et - i\text{-}Pr)^+$ (2), 238 $(M - 1 - 5\ Me)^+$ (100), 228 $(M + H - Et - Me - i\text{-}Pr)^+$ or $(M + 2 - CH(i\text{-}Pr)CH_2OH)^+$ (94),[81] 226 $(M - CH(i\text{-}Pr)CH_2OH)^+$ (2),

184 (M + 1 – Et – CH(*i*-Pr)CH_2OH – Me)$^+$ (92);[81] HRMS: calcd for $C_{16}H_{28}NO_5$ [(M + H)$^+$] 314.1967, found 314.1974.

*(4aR,5R,7S,8S,8aR)-8-Ethyl-3-((S)-1-hydroxy-3-methylbutan-2-yl)-7-methyl-5-phenethyltetrahydro-2H,5H-pyrano[3,4-e][1,3]oxazine-2,4(3H)-dione (**5ai**)*. Aldol **2l** (43 mg, 0.12 mmol) and acetaldehyde (0.05 mL of a 3.3 M solution in DCM, 0.18 mmol, 1.5 equiv) were submitted to the general procedure for the synthesis of the bicycles **5** (two-steps EAP) and yielded, after purification by flash chromatography (28 cm of height of silica gel, *n*-hexane/EtOAc 90/10), 3-(*N*-acyl-oxazolidin-2-one)-THP **21c** (6 mg, 12%, >95:5 dr) and title bicycle **5ai** (22 mg, 45%, >95:5 dr). Appearance: colorless oil; R_F: 0.60 (*n*-hexane/EtOAc 70/30 three times); $[\alpha]^{25}_D$ +97.7 (*c* 0.9, $CHCl_3$); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.82 (d, *J* = 6.7 Hz, 3H, $(C\underline{H}_3)_2CH$), 0.92 (t, *J* = 7.5 Hz, 3H, $H_{2'''}$), 1.04 (d, *J* = 6.7 Hz, 3H, $(C\underline{H}_3)_2CH$), 1.32 (d, *J* = 6.1 Hz, 3H, $H_{1''}$), 1.55-1.63 (m, 2H, H_8, $H_{1'''}$), 1.68-1.76 (m, 1H, $H_{1'''}$), 1.81-1.88 (m, 1H, $H_{1'}$), 2.35-2.45 (m, $(CH_3)_2C\underline{H}$), 2.43 (dd, *J* = 12.0, 9.8 Hz, 1H, H_{4a}), 2.59-2.66 (m, 1H, $H_{1'}$), 2.71-2.77 (m, 1H, $H_{2'}$), 2.85-2.91 (m, 1H, $H_{2'}$), 3.25 (dq, *J* = 9.8, 6.3 Hz, 1H, H_7), 3.47 (td, *J* = 9.5, 2.2 Hz, 1H, H_5), 3.78 (dd, *J* = 12.2, 2.8 Hz, 1H, $C\underline{H}_2OH$), 4.03 (dd, *J* = 12.2, 7.5 Hz, 1H, $C\underline{H}_2OH$), 4.10 (dd, *J* = 11.9, 10.4 Hz, 1H, H_{8a}), 4.32-4.38 (m, 1H, $NC\underline{H}$(*i*-Pr)CH_2OH), 7.16-7.20 (m, 1H, Ph), 7.21-7.24 (m, 2H, Ph), 7.26-7.30 (m, 2H, Ph); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.7 (q, $C_{2'''}$), 19.0 (t, $C_{1'''}$), 19.1 (q, $C_{1''}$), 20.0 (q, $(\underline{C}H_3)_2CH$), 20.2 (q, $(\underline{C}H_3)_2CH$), 25.3 (d, $(CH_3)_2\underline{C}H$), 31.5 (t, $C_{2'}$), 35.7 (t, $C_{1'}$), 47.1 (d, C_8), 47.6 (d, C_{4a}),[82] 62.7 (t, $\underline{C}H_2OH$), 73.7 (d, C_5), 73.9 (d, C_7), 76.7 (d, C_{8a}), 125.9 (d, Ph), 128.5 (d, 2C, Ph), 128.8 (d, 2C, Ph), 141.9 (s, Ph), 152.3 (s, C_2), 169.8 (s, C_4); MS (EI) m/z (relative intensity): 403 (M)$^+$ (13), 385 (M – H_2O)$^+$ (2),[83] 283 (M – CH_2OH)$^+$ (1), 359 (M + H – *i*-Pr)$^+$ (2), 316 (M –

$CH(i\text{-}Pr)CH_2OH)^+$ (4), 298 $(M - CH_2CH_2Ph)^+$ (22), 256 $(M + H - CH_2CH_2Ph - i\text{-}Pr)^+$ (18);[83] HRMS: calcd for $C_{23}H_{33}NO_5$ $[(M)^+]$ 403.2359, found 403.2385.

Synthesis of the 2-oxonia-Cope rearranged isomers 6. These by-products could be punctually detected during the synthesis of the bicycles **5**. **6a** and **6c** were described in our previous publication,[30] and **6b**, **6x** and **6y** were never isolated.

color

Synthesis of the halogenated 2,3,4,5,6-pentasubstituted THPs 1 and 7.

(4aS,5S*,7R*,8R*,8aS*)-3-(2-Chloroethyl)-8-ethyl-5,7-diisobutyltetrahydro-2H,5H-pyrano[3,4-e][1,3]oxazine-2,4(3H)-dione (**7a-Cl**)*. To a suspension of bicycle **5a** (86 mg, 0.24 mmol) in H_2O (2.4 mL, 0.1 M) was added a 37% HCl aqueous solution (2.4 mL, 29 mmol, 121 equiv) and the mixture was heated at 100 ºC. After 4 h, the mixture was allowed to cool to rt, saturated with NaCl and extracted with EtOAc (5 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (21 cm of height of silica gel, *n*-hexane/EtOAc 93/7) to yield title compound **7a-Cl** (51 mg, 57%) as a colorless oil. R_F: 0.31 (*n*-hexane/EtOAc 90/10); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.85-0.94 (m, 15H, 2x($C\underline{H}_3)_2CHCH_2$, $H_{2'''}$), 1.30-1.36 (m, 1H, $(CH_3)_2CHC\underline{H}_2$), 1.41-1.52 (m, 1H, $(CH_3)_2CHC\underline{H}_2$), 1.53-1.67 (m, 2H, H_8, $H_{1'''}$), 1.68-1.78 (m, 1H, $H_{1'''}$), 1.85-1.97 (m, 2H, 2x$(CH_3)_2C\underline{H}CH_2$), 2.07-2.13 (m, 1H, $(CH_3)_2CHC\underline{H}_2$), 2.38 (dd, J = 12.0, 9.6 Hz, 1H, H_{4a}), 3.19 (td, J = 10.3, 2.1 Hz, 1H, H_7), 3.53 (td, J = 10.1, 1.9 Hz, 1H, H_5), 3.69 (t, J = 6.3 Hz, $NCH_2C\underline{H}_2Cl$), 4.01-4.07 (m, 1H, $NC\underline{H}_2CH_2Cl$), 4.13-4.18 (m, 1H, $NC\underline{H}_2CH_2Cl$), 4.21 (dd, J = 11.7, 10.4 Hz, 1H, H_{8a}); ^{1}H-NMR (500 MHz, δ, C_6D_6): 0.69 (t, J = 7.5 Hz, 3H, $H_{2'''}$), 0.81 (d, J = 6.6 Hz, 3H, $(C\underline{H}_3)_2CHCH_2$), 0.87 (d, J = 6.8 Hz, 3H, $(C\underline{H}_3)_2CHCH_2$), 0.98 (d, J = 6.7 Hz, 3H, $(C\underline{H}_3)_2CHCH_2$), 1.00 (d, J = 6.6 Hz, 3H,

($C\underline{H}_3)_2CHCH_2$), 1.09 (ddd, J = 13.5, 10.5, 2.3 Hz, 1H, $H_{1''}$), 1.20-1.35 (m, 3H, H_8, $H_{1''}$, $H_{1'''}$), 1.36-1.54 (m, 2H, $H_{1'}$, $H_{1'''}$), 1.70 (dd, J = 12.0, 9.6 Hz, 1H, H_{4a}), 1.89-1.99 (m, 1H, $H_{2''}$), 2.00-2.09 (m, 1H, $H_{2'}$), 2.22 (ddd, J = 13.6, 10.4, 1.9 Hz, 1H, $H_{1'}$), 2.72 (td, J = 10.5, 1.5 Hz, 1H, H_7), 3.20 (td, J = 9.8, 1.9 Hz, 1H, H_5), 3.37-3.48 (m, 2H, $NCH_2C\underline{H}_2Cl$), 3.64 (dd, J = 11.9, 10.4 Hz, 1H, H_{8a}), 3.81 (dt, J = 13.9, 6.1 Hz, 1H, $NC\underline{H}_2CH_2Cl$), 3.97 (dt, J = 13.9, 6.7 Hz, 1H, $NC\underline{H}_2CH_2Cl$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.3 (q, $C_{2'''}$), 18.5 (t, $C_{1'''}$), 21.0 (q, $(\underline{C}H_3)_2CHCH_2$), 21.1 (q, $(\underline{C}H_3)_2CHCH_2$), 23.9 (q, $(\underline{C}H_3)_2CHCH_2$), 24.0 (q, $(\underline{C}H_3)_2CHCH_2$), 24.1 (d, $(CH_3)_2\underline{C}HCH_2$), 24.3 (d, $(CH_3)_2\underline{C}HCH_2$), 40.7 (t, $NCH_2\underline{C}H_2Cl$), 41.5 (t, $(CH_3)_2CH\underline{C}H_2$), 42.9 (t, $N\underline{C}H_2CH_2Cl$), 43.4 (t, $(CH_3)_2CH\underline{C}H_2$), 45.6 (d, C_8), 48.1 (d, C_{4a}), 72.8 (d, C_5), 75.1 (d, C_7), 76.8 (d, C_{8a}), 151.4 (s, C_2), 168.7 (s, C_4); ^{13}C-NMR (125 MHz, δ, C_6D_6): 10.0 (q, $C_{2'''}$), 19.1 (t, $C_{1'''}$), 21.3 (q, $(\underline{C}H_3)_2CHCH_2$), 21.6 (q, $(\underline{C}H_3)_2CHCH_2$), 24.0 (q, 2C, 2x$(\underline{C}H_3)_2CHCH_2$), 24.4 (d, $C_{2''}$), 24.9 (d, $C_{2'}$), 41.0 (t, $NCH_2\underline{C}H_2Cl$), 42.0 (t, $C_{1''}$), 42.9 (t, $N\underline{C}H_2CH_2Cl$), 43.9 (t, $C_{1'}$), 46.1 (d, C_8), 47.9 (d, C_{4a}), 72.9 (d, C_5), 75.3 (d, C_7), 76.9 (d, C_{8a}), 150.8 (s, C_2), 168.6 (s, C_4); MS (EI) m/z (relative intensity): 375 (^{37}Cl-M)$^+$ (1), 373 (^{35}Cl-M)$^+$ (3), 316 (M – *i*-Bu)$^+$ (100), 287 (M – *i*-Bu – Et)$^+$ (9), 259 (M – 2 *i*-Bu)$^+$ (17); HRMS: calcd for $C_{19}H_{32}NO_4Cl$ [(M)$^+$] 373.2020, found 373.2014; HRMS: calcd for $C_{19}H_{32}NO_4Na^{37}Cl$ [(M + Na)$^+$] 398.1888, found 398.1898.

*(4aS,5S,7R,8R,8aS)-3-(2-Bromoethyl)-8-ethyl-5,7-diisobutyltetrahydro-2H,5H-pyrano[3,4-e][1,3]oxazine-2,4(3H)-dione (**7a-Br**)*. To a suspension of bicycle **5a** (1.55 g, 4.3 mmol) in H_2O (4.3 mL, 0.1 M) was added a 48 % HBr aqueous solution (58.5 mL, 520 mmol, 121 equiv) and the mixture was heated at 100 ºC. After 24 h, the mixture was allowed to cool to rt, saturated with NaCl and extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (6 cm of height of silica gel, *n*-hexane/EtOAc 60/40)

to yield title compound **7a-Br** (1.45 g, 81%) as a thick brown oil. R_F: 0.3 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.84-0.88 (m, 3H, $H_{2'''}$), 0.90-0.97 (m, 12H, 4x($C\underline{H}_3$)$_2$CH), 1.30-1.37 (m, 1H, $H_{1''}$), 1.40-1.50 (m, 2H, $H_{1'}$, $H_{1''}$), 1.52-1.65(m, 2H, H_8, $H_{1'''}$), 1.70-1.76 (m, 1H, $H_{1'''}$), 1.85-1.96 (m, 2H, $H_{2'}$, $H_{2''}$), 2.06-2.14 (m, 1H, $H_{1'}$), 2.34-2.40 (m, 1H, H_{4a}), 3.16-3.23 (m, 1H, H_7), 3.49-3.56 (m, 3H, H_5, $NCH_2C\underline{H}_2Br$), 4.05-4.14 (m, 1H, $NC\underline{H}_2CH_2Br$), 4.15-4.26 (m, 2H, H_{8a}, $NC\underline{H}_2CH_2Br$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.3 (q, $C_{2'''}$), 18.5 (t, $C_{1'''}$), 21.0 (q, ($\underline{C}H_3$)$_2$CHCH$_2$), 21.2 (q, ($\underline{C}H_3$)$_2$CHCH$_2$), 23.9 (q, ($\underline{C}H_3$)$_2$CHCH$_2$), 24.0 (q, ($\underline{C}H_3$)$_2$CHCH$_2$), 24.1 (d, (CH$_3$)$_2\underline{C}$HCH$_2$), 24.4 (d, (CH$_3$)$_2\underline{C}$HCH$_2$), 28.3 (t, $NCH_2\underline{C}H_2Br$), 41.6 (t, (CH$_3$)$_2$CH$\underline{C}$H$_2$), 42.8 (t, $N\underline{C}H_2CH_2Br$), 43.4 (t, (CH$_3$)$_2$CH$\underline{C}$H$_2$), 45.6 (d, C_8), 48.1 (d, C_{4a}), 72.9 (d, C_5), 75.2 (d, C_{8a}), 76.8 (d, C_7), 151.3 (s, C_2), 168.6 (s, C_4); HRMS: calcd for $C_{19}H_{32}BrNO_4Na$ [$(M + Na)^+$] 440.1392, found 440.1410.

(4aS,5S*,7R*,8R*,8aS*)-3-(2-Chloroethyl)-8-ethyl-5,7-dimethyltetrahydro-2H,5H-pyrano[3,4-e][1,3]oxazine-2,4(3H)-dione (7**b-Cl**)*. To a solution of aldol **2b** (37 mg, 0.16 mmol) in DCM (1.6 mL, 0.1 M) was sequentially added acetaldehyde (73 μL of a 3.3 M solution in DCM, 0.24 mmol, 1.5 equiv), TMSCl (0.05 mL, 0.40 mmol, 2.5 equiv) and $BF_3{\cdot}OEt_2$ (0.01 mL, 0.08 mmol, 0.5 equiv; lower amounts led to higher reaction times and worse yields of the bicycle). After 2 h, the reaction was quenched by adding H_2O (2 mL), the layers were separated and the aqueous layer was extracted with DCM (3 x 2 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (16 cm of height of silica gel, *n*-hexane/EtOAc 70/30) to yield title compound **7b-Cl** (31 mg, 67%, >95:5 dr) and rearranged by-product **6b** (2 mg, 6%). **7b-Cl** was isolated as a white solid and its description is given below. R_F: 0.60 (*n*-hexane/EtOAc 60/40); mp 53-57 ºC (from DCM/*n*-hexane); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.93 (t, J = 7.5 Hz, 3H, $H_{2'''}$), 1.28 (d,

J = 6.1 Hz, 3H, $H_{1''}$), 1.55 (d, J = 6.0 Hz, 3H, $H_{1'}$), 1.57-1.64 (m, 2H, H_8, $H_{1'''}$), 1.70-1.77 (m, 1H, $H_{1'''}$), 2.38 (dd, J = 12.1, 9.6 Hz, 1H, H_{4a}), 3.33 (dq, J = 9.8, 6.1 Hz, 1H, H_7), 3.62 (dq, J = 9.6, 6.0 Hz, 1H, H_5), 3.71 (t, J = 6.4 Hz, 2H, $NCH_2C\underline{H}_2Cl$), 4.08 (dt, J = 13.8, 6.3 Hz, 1H, $NC\underline{H}_2CH_2Cl$), 4.17 (dt, J = 13.9, 6.6 Hz, 1H, $NC\underline{H}_2CH_2Cl$), 4.19 (dd, J = 12.2, 10.3 Hz, 1H, H_{8a}); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.6 (q, $C_{2'''}$), 18.9 (t, $C_{1'''}$), 19.1 (q, $C_{1''}$), 21.0 (q, $C_{1'}$), 40.7 (t, $NCH_2\underline{C}H_2Cl$), 42.9 (t, $N\underline{C}H_2CH_2Cl$), 46.9 (d, C_8), 49.1 (d, C_{4a}), 71.1 (d, C_5), 73.9 (d, C_7), 76.5 (d, C_{8a}), 151.4 (s, C_4), 168.5 (s, C_2); MS (EI) m/z (relative intensity): 289 $(M)^+$ (4), 274 $(M - Me)^+$ (16), 246 $(M - Et - Me)^+$ (3), 230 $(M - 1 - Et - 2\ Me)^+$ (4); HRMS: calcd for $C_{13}H_{20}NO_4Na^{35}Cl$ $[(M + Na)^+]$ 312.0979, found 312.0970; HRMS: calcd for $C_{13}H_{20}NO_4{}^{35}Cl$ $[(M)^+]$ 289.1081, found 289.1089.

(4aS,5S*,7R*,8R*,8aS*)-3-(2-Bromoethyl)-8-ethyl-5,7-dimethyltetrahydro-2H,5H-pyrano[3,4-e][1,3]oxazine-2,4(3H)-dione (**7b-Br**) and 3-((2S*,3R*,4S*,5R*,6R*)-4-bromo-5-ethyl-2,6-dimethyltetrahydro-2H-pyran-3-carbonyl)oxazolidin-2-one (**1b-Br**)*. To a solution of aldol **2b** (50 mg, 0.22 mmol) and acetaldehyde (0.1 mL of a 3.3 M solution in DCM, 0.33 mmol, 1.5 equiv) in DCM (2.2 mL, 0.1 M) was added TMSBr (0.08 mL, 0.55 mmol, 2.5 equiv). After 3 h, the reaction was stopped by the addition of H_2O (3 mL) and the aqueous layer was extracted with DCM (3 x 3 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The ^{1}H-NMR analysis of the crude revealed a 1.5/1 mixture of the isomers **7b-Br** and **1b-Br**, respectively. Purification by flash chromatography (16 cm of height of silica gel, *n*-hexane/EtOAc 90/10) allowed their separation, yielding bicycle **7b-Br** (34 mg, 46%, >95:5 dr) and 3-(*N*-acyl oxazolidin-2-one)-THP **1b-Br** (22 mg, 30%, >95:5 dr). **7b-Br**: yellowish oil; R_F: 0.53 (*n*-hexane/EtOAc 80/20); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.92 (t, J = 7.5 Hz, 3H, $H_{2'''}$), 1.27 (d, J = 6.2 Hz, 3H, $H_{1''}$), 1.54 (d, J = 6.0 Hz, 3H, $H_{1'}$), 1.56-1.63 (m, 2H,

H_8, $H_{1'''}$), 1.69-1.77 (m, 1H, $H_{1'''}$), 2.36 (dd, J = 12.1, 9.8 Hz, 1H, H_{4a}), 3.32 (dq, J = 9.8, 6.1 Hz, 1H, H_7), 3.54 (t, J = 6.7 Hz, 2H, $NCH_2C\underline{H}_2Br$), 3.62 (dq, J = 9.7, 6.1 Hz, 1H, H_5), 4.09-4.14 (m, 1H, $NC\underline{H}_2CH_2Br$), 4.17-4.23 (m, 2H, H_{8a}, 1x$NC\underline{H}_2CH_2Br$); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 9.5 (q, $C_{2'''}$), 18.9 (t, $C_{1'''}$), 19.1 (q, $C_{1''}$), 20.9 (q, $C_{1'}$), 28.3 (t, $NCH_2\underline{C}H_2Br$), 42.7 (t, $N\underline{C}H_2CH_2Br$), 46.8 (d, C_8), 49.1 (d, C_{4a}), 71.0 (d, C_5), 73.9 (d, C_7), 76.5 (d, C_{8a}), 151.2 (s, C_2), 168.4 (s, C_4); MS (EI) m/z (relative intensity): 335 ($^{81}M)^+$ (4), 333 ($^{79}M)^+$ (3), 319 (^{81}M – Me)$^+$ (13), 317 (^{79}M – Me)$^+$ (13), 69 (100); HRMS: calcd for $C_{13}H_{20}{}^{81}BrNO_4$ [($^{81}M)^+$] 335.0555, found 335.0544. **1b-Br**: thick colorless oil; R_F: 0.25 (*n*-hexane/EtOAc 80/20), 0.58 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.87 (t, J = 7.6 Hz, 3H, $C_{5'}CH_2\underline{C}H_3$), 1.21 (d, J = 6.1 Hz, 3H, $C_{2'}\underline{C}H_3$), 1.28 (d, J = 6.1 Hz, 3H, $C_{6'}\underline{C}H_3$), 1.59-1.66 (m, 1H, $C_{5'}C\underline{H}_2CH_3$), 1.68-1.73 (m, 1H, $H_{5'}$), 1.76-1.84 (m, 1H, $C_{5'}C\underline{H}_2CH_3$), 3.47 (dq, J = 9.7, 6.2 Hz, 1H, $H_{6'}$), 3.60 (dq, J = 9.4, 6.2 Hz, 1H, $H_{2'}$), 4.04 (dt, J = 11.1, 8.3 Hz, 1H, H_4), 4.12 (dt, J = 11.1, 7.9 Hz, 1H, H_4), 4.38 (dd, J = 11.1, 11.1 Hz, 1H, $H_{4'}$), 4.43 (t, J = 8.2 Hz, 2H, H_5), 4.63 (dd, J = 10.2, 10.2 Hz, 1H, $H_{3'}$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 8.8 (q, $C_{5'}CH_2\underline{C}H_3$), 21.9 (t, $C_{5'}\underline{C}H_2CH_3$), 19.6 (q, $C_{2'}\underline{C}H_3$), 20.0 (q, $C_{6'}\underline{C}H_3$), 42.9 (t, C_4), 49.7 (d, $C_{5'}$), 55.7 (d, $C_{3'}$), 56.1 (d, $C_{4'}$), 61.9 (t, C_5), 76.1 (d, $C_{2'}$), 76.2 (d, $C_{6'}$), 153.1 (s, C_2), 172.5 (s, $C_{3'}\underline{C}$(O)N); MS (EI) m/z (relative intensity): 254 (M – Br)$^+$ (26), 210 (M – 1 – Br – Et – Me)$^+$ (100), 168 (M – Br – oxazolidin-2-one)$^+$ (3), 140 (M – Br – *N*-acyl oxazolidin-2-one)$^+$ (1); HRMS: calcd for $C_{13}H_{20}{}^{79}BrNO_4Na$ [(^{79}M + Na)$^+$] 356.0473, found 356.0477.

(4aS,5S*,7R*,8R*,8aS*)-8-Ethyl-3-(2-iodoethyl)-5,7-dimethyltetrahydro-2H,5H-pyrano[3,4-e][1,3]oxazine-2,4(3H)-dione (**7b-I**) and 3-((2S*,3R*,4S*,5R*,6R*)-5-ethyl-4-iodo-2,6-dimethyltetrahydro-2H-pyran-3-carbonyl)oxazolidin-2-one (**1b-I**)*. To a solution of aldol **2b** (50 mg, 0.22 mmol) and acetaldehyde (0.1 mL of a 3.3 M solution

in DCM, 0.33 mmol, 1.5 equiv) in DCM (2.2 mL, 0.1 M) was added TMSI (0.08 mL, 0.55 mmol, 2.5 equiv). TLC analysis showed that the reaction was completed at 12 min, and H_2O (3 mL) was added. The aqueous layer was extracted with DCM (3 x 3 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The ^{1}H-NMR analysis of the crude revealed a 3.4/1 mixture of the isomers **7b-I** and **1b-I**, respectively. Purification by flash chromatography (16 cm of height of silica gel, *n*-hexane/EtOAc 90/10) allowed their separation, yielding bicycle **7b-I** (50 mg, 58%, >95:5 dr) and 3-(*N*-acyl oxazolidin-2-one)-THP **1b-I** (14 mg, 17%, >95:5 dr). **7b-I**: yellow oil; R_F: 0.22 (*n*-hexane/EtOAc 90/10), 0.63 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.94 (t, J = 7.5 Hz, 3H, $H_{2'''}$), 1.27 (d, J = 6.2 Hz, 3H, $H_{1''}$), 1.54 (d, J = 6.0 Hz, 3H, $H_{1'}$), 1.56-1.65 (m, 2H, H_8, $H_{1'''}$), 1.69-1.76 (m, 1H, $H_{1'''}$), 2.34 (dd, J = 12.1, 9.6 Hz, 1H, H_{4a}), 3.29-3.37 (m, 3H, H_7, 2x$NCH_2C\underline{H}_2I$), 3.61 (dq, J = 9.7, 6.0 Hz, 1H, H_5), 4.03-4.08 (m, 1H, $NC\underline{H}_2CH_2I$), 4.11-4.16 (m, 1H, $NC\underline{H}_2CH_2I$), 4.20 (dd, J = 11.8, 10.7 Hz, 1H, H_{8a}); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 0.3 (t, $NCH_2\underline{C}H_2I$), 9.7 (q, $C_{2'''}$), 19.11 (t, $C_{1'''}$), 19.13 (q, $C_{1''}$), 21.0 (q, $C_{1'}$), 43.5 (t, $N\underline{C}H_2CH_2I$), 47.1 (d, C_8), 49.4 (d, C_{4a}), 71.2 (d, C_5), 74.1 (d, C_7), 76.8 (d, C_{8a}), 151.1 (s, C_2), 168.3 (s, C_4); MS (EI) m/z (relative intensity): 267 (3), 254 $(M - I)^+$ (5), 228 $(M + 2 - CH_2CH_2I)^+$ (1), 210 $(M - CH_2CH_2I - Me)^+$ or $(M - Et - I - Me)^+$ (56), 184 $(M - CH_2CH_2I - Et - Me)^+$ (1), 140, 91 (100); HRMS: calcd for $C_{13}H_{20}NO_4$ $[(M - I)^+]$ 254.1392, found 254.1384. **1b-I**: yellow oil; R_F: 0.07 (*n*-hexane/EtOAc 90/10), 0.44 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.83 (t, J = 7.5 Hz, 3H, $C_{5'}CH_2C\underline{H}_3$), 1.20 (d, J = 6.2 Hz, 3H, $C_{2'}C\underline{H}_3$), 1.28 (d, J = 6.2 Hz, 3H, $C_{6'}C\underline{H}_3$), 1.62-1.68 (m, 1H, 1x$C_{5'}C\underline{H}_2CH_3$), 1.70-1.79 (m, 2H, $H_{5'}$, 1x$C_{5'}C\underline{H}_2CH_3$), 3.49 (dq, J = 9.4, 6.1 Hz, 1H, $H_{6'}$), 3.58 (dq, J = 9.4, 6.1 Hz, 1H, $H_{2'}$), 4.01-4.07 (m, 1H, H_4), 4.09-4.14 (m, 1H, H_4), 4.40-4.47 (m, 3H, 2xH_5, $H_{4'}$), 4.77 (dd, J = 11.0, 10.1 Hz, 1H, $H_{3'}$); ^{13}C-NMR (150 MHz, δ, $CDCl_3$):

8.5 (q, $C_{5'}CH_2\underline{C}H_3$), 19.7 (q, $C_2\underline{C}H_3$), 20.3 (q, $C_6\underline{C}H_3$), 24.8 (t, $C_{5'}\underline{C}H_2CH_3$), 36.6 (d, $C_{4'}$), 42.9 (t, C_4), 50.0 (d, $C_{5'}$), 57.0 (d, $C_{3'}$), 61.9 (t, C_5), 76.1 (d, $C_{6'}$), 77.0 (d, $C_{2'}$), 153.0 (s, C_2), 173.2 (s, $C_3\underline{C}O$); MS (EI) m/z (relative intensity): 295 (M – oxazolidin-2-one)$^+$ (1), 267 (M – N-acyl oxazolidin-2-one)$^+$ (1), 254 (M – I)$^+$ (33), 210 (M – CH_2CH_2I – Me)$^+$ or (M – Et – I – Me)$^+$ (100), 168 (M – I – oxazolidin-2-one)$^+$ (2), 140 (M – I – N-acyl oxazolidin-2-one)$^+$ (1); HRMS: calcd for $C_{13}H_{20}NO_4$ [(M – I)$^+$] 254.1392, found 254.1389.

Synthesis of the 2,3,4,5-tetrasubstituted THFs 8. These by-products were punctually obtained during the synthesis of the corresponding bicycles **5**.

3-((2S,3R*,4R*)-2-Methyl-4-((E)-prop-1-en-1-yl)-1-oxaspiro[4.5]decane-3-carbonyl)oxazolidin-2-one (**8l**)*. For the detailed synthetic procedure, see the synthesis of bicycle **5l**. THF **8l** (7.8 mg, 19%, 80:20 dr) was isolated as a white solid (probably crystalline); R_F: 0.43 (*n*-hexane/EtOAc 80/20 four times); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 1.09-1.14 (m, 1H, CH_2 from cyclohexane), 1.23-1.26 (m, 1H, $C\underline{H}_2$ from cyclohexane), 1.28 (d, J = 6.1 Hz, 3H, $C_{2'}\underline{Me}$), 1.39-1.45 (m, 1H, $C\underline{H}_2$ from cyclohexane), 1.50-1.55 (m, 2H, $C\underline{H}_2$ from cyclohexane), 1.56-1.62 (m, 5H, $C\underline{H}_2$ from cyclohexane), 1.62 (dd, J = 6.0, 1.0 Hz, 3H, $C_{4'}CH{=}CH\underline{Me}$), 2.79 (dd, J = 11.1, 8.9 Hz, 1H, $H_{4'}$), 4.02 (t, J = 8.0 Hz, 2H, H_4), 4.20 (dq, J = 9.3, 6.1 Hz, 1H, $H_{2'}$), 4.33-4.41 (m, 3H, 2xH_5, $H_{3'}$), 5.36-5.48 (m, 2H, $C_{4'}C\underline{H}{=}C\underline{H}Me$); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 18.2 (q, $C_{4'}CH{=}CH\underline{Me}$), 21.0 (q, $C_{2'}\underline{Me}$), 21.8 (t, $\underline{C}H_2$ from cyclohexane), 23.3 (t, $\underline{C}H_2$ from cyclohexane), 25.8 (t, $\underline{C}H_2$ from cyclohexane), 34.5 (t, $\underline{C}H_2$ from cyclohexane), 36.7 (t, $\underline{C}H_2$ from cyclohexane), 43.1 (t, C_4), 53.7 (d, $C_{3'}$), 60.9 (d, $C_{4'}$), 61.8 (t, C_5),

77.1 (d, $C_{2'}$), 84.2 (s, $C_{5'}$), 128.1 (d, =CH), 128.4 (d, =CH), 153.4 (s, NC(O)O), 173.6 (s, $C_{3'}$C(O)N); HRMS: calcd for $C_{17}H_{25}NO_4Na$ [$(M + Na)^+$] 330.1681, found 330.1671.

3-((2S,3R*,4R*,5R*)-2-Methyl-5-phenyl-4-((E)-prop-1-en-1-yl)tetrahydrofuran-3-carbonyl)oxazolidin-2-one (**8m**)*. Aldol **2b** (110 mg, 0.48 mmol) was submitted to the general procedure for the synthesis of the bicycles **5** (two-steps EAP) and yielded, after purification by flash chromatography (28 cm of height of silica gel, *n*-hexane/EtOAc 60/40), title compound **8m** (6 mg, 4%, 80:20 dr) and bicycle **5i** (117 mg, 72%, >95:5 dr). THF **8m** was isolated as a thick colorless oil and its description is given below. R_F: 0.42 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 1.42 (dd, J = 6.5, 1.6 Hz, 3H, $C_{4'}$CH=CHCH$_3$), 1.49 (d, J = 5.7 Hz, 3H, $C_{2'}$CH$_3$), 3.46-3.50 (m, 1H, $H_{4'}$), 4.02-4.07 (m, 2H, H_4), 4.27-4.33 (m, 1H, $H_{3'}$), 4.36-4.47 (m, 3H, H_5, $H_{2'}$), 4.77-4.87 (m, 1H, $C_{4'}$CH=CHCH$_3$), 5.21 (d, J = 8.3 Hz, 1H, $H_{5'}$), 5.29-5.37 (m, 1H, $C_{4'}$CH=CHCH$_3$), 7.20-7.25 (m, 3H, Ar), 7.29-7.33 (m, 2H, Ar); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 17.8 (q, $C_{4'}$CH=CHCH$_3$), 19.7 (q, $C_{2'}$CH$_3$), 43.1 (t, C_4), 53.8 (d, $C_{4'}$), 54.8 (d, $C_{3'}$), 61.9 (t, C_5), 79.2 (d, $C_{2'}$), 83.8 (d, $C_{5'}$), 127.0 (d, 2C, Ar), 127.3 (d, Ar), 127.7 (d, $C_{4'}$CH=CHCH$_3$), 128.1 (d, 2C, Ar), 129.0 (d, $C_{4'}$CH=CHCH$_3$), 139.7 (s, Ar), 153.3 (s, C_2), 173.5 (s, $C_{3'}$C(O)N); HRMS: calcd for $C_{18}H_{21}NO_4Na$ [$(M + Na)^+$] 338.1368, found 338.1369.

*3-((2S,3R,4R,5S)-5-(3-fluorophenyl)-2-methyl-4-((E)-prop-1-en-1-yl)tetrahydrofuran-3-carbonyl)oxazolidin-2-one (**8n**)*. Aldol **2b** (56 mg, 0.25 mmol) was submitted to the general procedure for the synthesis of the bicycles **5** (two-steps EAP) and yielded, after purification by flash chromatography (28 cm of height of silica gel, *n*-hexane/EtOAc 70/30), title compound **8n** (7 mg, 8%, 85:15 dr) and bicycle **5n** (56 mg, 64%, >95:5 dr). THF **8n** was isolated as a thick colorless oil and its description is given below. R_F: 0.19 and 0.29 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 1.44 (dd, J = 6.5,

1.7 Hz, 3H, $C_{4'}CH=CHC\underline{H}_3$), 1.49 (d, J = 5.9 Hz, 3H, $C_{2'}C\underline{H}_3$), 3.44-3.50 (m, 1H, $H_{4'}$), 4.05 (t, J = 8.0 Hz, 2H, H_4), 4.21-4.48 (m, 4H, 2xH_5, $H_{2'}$, $H_{3'}$), 4.78-4.86 (m, 1H, $C_{4'}C\underline{H}=CHCH_3$), 5.19 (d, J = 8.0 Hz, 1H, $H_{5'}$), 5.30-5.38 (m, 1H, $C_{4'}CH=C\underline{H}CH_3$), 6.90-7.03 (m, 4H, Ar), 7.10-7.15 (m, 1H, Ar); once the ^{1}H-NMR spectrum was recorded, the solvent was evaporated and the product was stored at –18 ºC under Ar atmosphere. 12 months later, the NMR analysis showed that the product had suffered decomposition, thus a well-resolved ^{13}C-NMR spectrum could not be obtained; HRMS: calcd for $C_{18}H_{20}NO_4FNa$ [$(M + Na)^+$] 356.1274, found 356.1281.

3-((2S,3R*,4R*,5S*)-5-(2-Chlorophenyl)-2-methyl-4-((E)-prop-1-en-1-yl)tetrahydrofuran-3-carbonyl)oxazolidin-2-one* ***(8o)***. Aldol **2b** (102 mg, 0.45 mmol) was submitted to the general procedure for the synthesis of the bicycles **5** (two-steps EAP) and yielded, after purification by flash chromatography (21 cm of height of silica gel, *n*-hexane/EtOAc 70/30), title compound **8o** (25 mg, 16%, 80:20 dr), bicycle **5o** (100 mg, 60%, >95:5 dr) and bicycle **5b** (1 mg, 1%, >95:5 dr). THF **8o** was isolated as a thick yellowish oil and its description is given below. R_F: 0.37 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 1.37 (dd, J = 6.5, 1.6 Hz, 3H, $C_{4'}CH=CHC\underline{H}_3$), 1.50 (d, J = 6.0 Hz, 3H, $C_{2'}C\underline{H}_3$), 3.62 (dt, J = 9.7, 7.3 Hz, 1H, $H_{4'}$), 4.07 (t, J = 7.9 Hz, 2H, H_4), 4.24 (dd, J = 7.9, 6.6 Hz, 1H, $H_{3'}$), 4.30 (dq, J = 8.1, 6.0 Hz, 1H, $H_{2'}$), 4.37-4.44 (m, 2H, H_5), 4.87 (ddq, J = 15.1, 9.8, 1.6 Hz, 1H, $C_{4'}C\underline{H}=CHCH_3$), 5.34 (dq, J = 14.9, 6.3 Hz, 1H, $C_{4'}CH=C\underline{H}CH_3$), 5.51 (d, J = 7.6 Hz, 1H, $H_{5'}$), 7.15-7.19 (m, 1H, Ar), 7.25-7.29 (m, 2H, Ar), 7.54-57 (m, 2H); ^{1}H-NMR (500 MHz, δ, C_6D_6): 1.26 (dd, J = 6.5, 1.6 Hz, 3H, $C_{4'}CH=CHC\underline{H}_3$), 1.61 (d, J = 6.1 Hz, 3H, $C_{2'}C\underline{H}_3$), 2.90-3.00 (m, 4H, 2xH_4, 2xH_5), 3.99 (ddd, J = 9.6, 6.9, 6.9 Hz, 1H, $H_{4'}$), 4.44 (dd, J = 7.7, 6.1 Hz, 1H, $H_{2'}$), 4.62 (dd, J = 7.7, 6.4 Hz, 1H, $H_{3'}$), 5.18 (ddd, J = 15.2, 10.0, 1.6 Hz, 1H, $C_{4'}C\underline{H}=CHCH_3$), 5.49 (dq, J = 15.2, 6.5 Hz, 1H, $C_{4'}CH=C\underline{H}CH_3$), 5.81 (d, J = 7.6 Hz, 1H, $H_{5'}$), 6.79 (td, J = 7.7,

1.6 Hz, 1H, Ar), 6.99 (td, J = 7.6, 1.0 Hz, 1H, Ar), 7.12 (dd, J = 7.9, 1.1 Hz, 1H, Ar), 7.81 (dd, J = 7.8, 1.4 Hz, 1H, Ar); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 17.7 (q, $C_{4'}CH{=}CH\underline{C}H_3$), 19.8 (q, $C_{2'}\underline{C}H_3$), 43.1 (t, C_4), 52.8 (d, $C_{4'}$), 54.8 (d, $C_{3'}$), 61.9 (t, C_5), 79.0 (d, $C_{2'}$), 80.8 (d, $C_{5'}$), 126.6 (d, Ar), 127.6 (d, $C_{4'}CH{=}\underline{C}HCH_3$), 127.9 (d, Ar), 128.3 (d, Ar), 128.6 (d, $C_{4'}\underline{C}H{=}CHCH_3$), 129.0 (d, Ar), 131.8 (s, Ar), 137.3 (s, Ar), 153.3 (s, C_2), 173.6 (s, $C_{3'}\underline{C}(O)N$); MS (EI) m/z (relative intensity): 350 $(M + 1)^+$ (1), 349 $(M)^+$ (1), 308 $(M - CH_3CH{=}CH)^+$ (1), 262 (M – 1 – oxazolidin-2-one)$^+$ (2), 235 (M – *N*-acyl oxazolidin-2-one)$^+$ (1), 193 (M – 1 – $CH_3CH{=}CH$ – *N*-acyl oxazolidin-2-one)$^+$ (24), 122 (M – 2 – Ar – *N*-acyl oxazolidin-2-one)$^+$ (100); HRMS: calcd for $C_{18}H_{20}NO_4Cl$ $[(M)^+]$ 349.1081, found 349.1097.

*3-((2S,3R,4R,5S)-5-(4-methoxyphenyl)-2-methyl-4-((E)-prop-1-en-1-yl)tetrahydrofuran-3-carbonyl)oxazolidin-2-one (**8q**)*. Aldol **2b** (119 mg, 0.53 mmol) was submitted to the general procedure for the synthesis of the bicycles **5** (two-steps EAP) and yielded, after purification by flash chromatography (28 cm of height of silica gel, *n*-hexane/EtOAc 60/40), title compound **8q** (18 mg, 10%, 80:20 dr), bicycle **5q** (119 mg, 63%, >95:5 dr) and bicycle **5b** (8 mg, 12%, >95:5 dr). THF **8q** was isolated as a thick yellowish oil and its description is given below. R_F: 0.51 (*n*-hexane/EtOAc 60/40 two times); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 1.40 (d, J = 6.2 Hz, 3H, $C_{4'}CH{=}CHC\underline{H}_3$), 1.59 (d, J = 6.3 Hz, 3H, $C_{2'}C\underline{H}_3$), 3.15-3.20 (m, 1H, $H_{4'}$), 3.80 (s, 3H, MeO), 4.05 (t, J = 8.0 Hz, 2H, H_4), 4.10-4.14 (m, 1H, $H_{2'}$), 4.39-4.47 (m, 3H, H_5, $H_{3'}$), 4.72 (d, J = 9.4 Hz, 1H, $H_{5'}$), 5.28-5.34 (m, 1H, $C_{4'}CH{=}C\underline{H}Me$), 5.40-5.45 (m, 1H, $C_{4'}C\underline{H}{=}CHMe$), 6.86 (d, J = 8.8 Hz, 2H, Ar), 7.28 (d, J = 8.8 Hz, 2H, Ar); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 18.1 (q, $C_{4'}CH{=}CH\underline{C}H_3$), 20.6 (q, $C_{2'}\underline{C}H_3$), 43.1 (t, C_4), 55.4 (q, MeO), 55.6 (d, $C_{3'}$), 58.6 (d, $C_{4'}$), 62.0 (t, C_5), 80.9 (d, $C_{2'}$), 85.2 (d, $C_{5'}$), 113.8 (d, 2C, Ar), 127.87 (d, 2C, Ar), 127.93 (d, $C_{4'}C\underline{H}{=}CHMe$), 129.1 (d, $C_{4'}CH{=}C\underline{H}Me$), 131.2 (s, Ar), 153.4 (s, C_2), 159.3

(s, Ar), 172.9 (s, $C_{3'}$C(O)N); HRMS: calcd for $C_{19}H_{23}NO_5Na$ [$(M + Na)^+$] 368.1474, found 368.1485.

3-((2S,3R*,4R*,5R*)-5-(2-Methoxyphenyl)-2-methyl-4-((E)-prop-1-en-1-yl)tetrahydrofuran-3-carbonyl)oxazolidin-2-one (**8r**)*. For the detailed synthetic procedure, see the synthesis of bicycle **5r**. THF **8r** (3 mg, 10%, >95:5 dr) was isolated as a thick colorless oil and its description is given below. R_F: 0.41 (*n*-hexane/EtOAc 60/40 two times); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 1.37 (dd, J = 6.5, 1.7 Hz, 3H, $C_{4'}$CH=CHMe), 1.48 (d, J = 5.8 Hz, 3H, $C_{2'}$Me), 3.49-3.54 (m, 1H, $H_{4'}$), 3.75 (s, 3H, MeO), 4.03-4.07 (m, 2H, H_4), 4.22-4.29 (m, 1H, $H_{3'}$), 4.34-4.43 (m, 3H, H_5, $H_{2'}$), 4.89 (ddq, J = 15.1, 9.6, 1.8 Hz, 1H, $C_{4'}$CH=CHMe), 5.21-5.31 (m, 1H, $C_{4'}$CH=CHMe), 5.46 (d, J = 7.8 Hz, 1H, $H_{5'}$), 6.77-6.79 (m, 1H, Ar), 6.93-6.96 (m, 1H, Ar), 7.18-7.22 (m, 1H, Ar), 7.41-7.43 (m, 1H, Ar); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 17.7 (q, $C_{4'}$CH=CHCH_3), 19.7 (q, $C_{2'}$$CH_3$), 43.1 (t, C_4), 53.3 (d, $C_{4'}$), 54.6 (d, $C_{3'}$), 55.2 (q, MeO), 61.8 (t, C_5), 78.8 (d, $C_{2'}$), 79.3 (d, $C_{5'}$), 109.8 (d, Ar), 120.4 (d, Ar), 126.4 (d, $C_{4'}$CH=$CHCH_3$), 127.0 (d, Ar), 128.1 (d, Ar), 128.2 (s, Ar), 130.0 (d, $C_{4'}$CH=$CHCH_3$), 153.2 (s, C_2), 156.0 (s, Ar), 174.0 (s, $C_{3'}$C(O)N); MS (EI) m/z (relative intensity): $(M)^+$ (1), 303 $(M - 1 - CH_3CH=CH)^+$ (1), 259 $(M$ – oxazolidin-2-one$)^+$ (1), 197 $(M - Ar - CH_3CH=CH)^+$ (1), 122 $(M - 2 - Ar -$ *N*-acyl oxazolidin-2-one$)^+$ (100); HRMS: calcd for $C_{19}H_{23}NO_5Na$ [$(M + Na)^+$] 368.1474, found 368.1474.

Ethyl (*R,*E*)-2-((*S**)-1-hydroxy-3-methylbutyl)hex-3-enoate (*syn*-9a) and ethyl (*S**,*E*)-2-((*S**)-1-hydroxy-3-methylbutyl)hex-3-enoate (*anti*-9a)**. All the subsequent operations were carried out under an Ar atmosphere. To an ice-cooled solution of *i*-Pr_2NH (1.44 mL, 10.27 mmol, 1.2 equiv) in THF (43 mL, 0.2 M regarding to the ester) was added a 2.5 M solution of *n*-butyllithium in hexanes (3.8 mL, 9.5 mmol, 1.1 equiv). The mixture was stirred at rt for 15 min, and then cooled to –78 ºC. A

solution of commercial ethyl (*E*)-hex-3-enoate (1.4 mL, 8.56 mmol) in THF (43 mL, 0.2 M) was dropwise added and the mixture was keeped at that temperature for 30 min. After that, a solution of *i*-BuCHO (1.1 mL, 10.27 mmol, 1.2 equiv) in THF (43 mL, 0.2 M regarding to the ester) was dropwise added and the mixture was allowed to warm to rt. After 12 h, a saturated NH_4Cl aqueous solution (150 mL) was added and the mixture was poured into a separatory funnel where the layers were separated. The aqueous layer was extracted with EtOAc (3 x 150 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to provide a 2.2/1 mixture of the *syn*/*anti* aldols (69:31 dr). Purification by flash chromatography (28 cm of height of silica gel, *n*-hexane/EtOAc 95/5) allowed the isolation of aldols ***syn*-9a** (1.06 g, 57%) and ***anti*-9a** (482 mg, 26%), both as yellowish oils. ***syn*-9a**: R_F: 0.61 (*n*-hexane/EtOAc 80/20); ^{1}H-NMR (400 MHz, δ, $CDCl_3$): 0.88 (d, J = 6.8 Hz, 3H, $C_{3'}(C\underline{H}_3)_2$), 0.90 (d, J = 6.8 Hz, 3H, $C_{3'}(C\underline{H}_3)_2$), 0.99 (t, J = 7.5 Hz, 3H), 1.10 (ddd, J = 13.9, 8.9, 3.5 Hz, 1H, $H_{2'}$), 1.25 (t, J = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.41 (ddd, J = 14.0, 9.5, 5.1 Hz, 1H, $H_{2'}$), 1.73-1.84 (m, 1H, $H_{3'}$), 2.04-2.11 (m, 2H, H_5), 2.60 (br s, 1H, OH), 2.92 (dd, J = 9.1, 4.7 Hz, 1H, H_2), 3.90-3.94 (m, 1H, $H_{1'}$), 4.15 (q, J = 7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.51 (dd, J = 15.7, 9.3 Hz, 1H, H_3), 5.67 (dt, J = 15.5, 6.5 Hz, 1H, H_4); ^{13}C-NMR (100 MHz, δ, $CDCl_3$): 13.6 (q, C_6), 14.3 (q, $CO_2CH_2\underline{C}H_3$), 21.9 (q, $C_{3'}(CH_3)_2$), 23.6 (q, $C_{3'}(CH_3)_2$), 24.5 (d, $C_{3'}$), 25.8 (t, C_5), 43.3 (t, $C_{2'}$), 55.4 (d, C_2), 60.9 (t, $CO_2\underline{C}H_2CH_3$), 66.7 (d, $C_{1'}$), 122.3 (d, C_3), 138.6 (d, C_4), 174.1 (s, C_1); MS (EI) m/z (relative intensity): 211 $(M - OH)^+$ (1), 171 $(M - i\text{-}Bu)^+$ (1), 155 $(M - CO_2Et)^+$ (2), 142 $(M + 1 - CH(OH)CH_2CH(CH_3)_2)^+$ (100); HRMS: calcd for $C_8H_{14}O_2$ $[(M + 1 - CH(OH)CH_2CH(CH_3)_2)^+]$ 142.0994, found 142.0990. ***anti*-9a**: R_F: 0.49 (*n*-hexane/EtOAc 80/20); ^{1}H-NMR (400 MHz, δ, $CDCl_3$): 0.89 (d, J = 6.8 Hz, 3H, $C_{3'}(C\underline{H}_3)_2$), 0.91 (d, J = 6.8 Hz, 3H, $C_{3'}(C\underline{H}_3)_2$), 0.98 (t, J = 7.5 Hz, 3H), 1.22-1.35 (m,

2H, $H_{2'}$), 1.26 (t, J = 7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.79-1.89 (m, 1H, $H_{3'}$), 2.01-2.09 (m, 2H, H_5), 2.40 (br s, 1H, OH), 2.98 (dd, J = 8.9, 7.4 Hz, 1H, H_2), 3.82-3.88 (br m, 1H, $H_{1'}$), 4.13-4.20 (m, 2H, $CO_2C\underline{H}_2CH_3$), 5.42 (ddt, J = 15.4, 9.0, 1.5 Hz, 1H, H_3), 5.67 (dt, J = 15.4, 6.4 Hz, 1H, H_4); ^{13}C-NMR (100 MHz, δ, $CDCl_3$): 13.6 (q, C_6), 14.3 (q, $CO_2CH_2\underline{C}H_3$), 21.7 (q, $C_{3'}(CH_3)_2$), 23.8 (q, $C_{3'}(CH_3)_2$), 24.6 (d, $C_{3'}$), 25.7 (t, C_5), 44.0 (t, $C_{2'}$), 56.4 (d, C_2), 60.8 (t, $CO_2\underline{C}H_2CH_3$), 71.1 (d, $C_{1'}$), 123.6 (d, C_3), 137.4 (d, C_4), 174.0 (s, C_1); MS (EI) m/z (relative intensity): 211 $(M - OH)^+$ (1), 171 $(M - i\text{-Bu})^+$ (2), 155 $(M - CO_2Et)^+$ (2), 142 $(M + 1 - CH(OH)CH_2CH(CH_3)_2)^+$ (100); HRMS: calcd for $C_8H_{14}O_2$ [$(M + 1 - CH(OH)CH_2CH(CH_3)_2)^+$] 142.0994, found 142.0989.

Methyl (*R,*E*)-2-((*S**)-1-hydroxyethyl)hex-3-enoate (*syn*-9b)**. To a solution of the aldol **2b** (29 mg, 0.13 mmol) in DCM (1.3 mL, 0.1 M) was sequentially added, under Ar atmosphere, MeOH (0.11 mL, 2.60 mmol, 20 equiv) and $FeCl_3$ (52.7 mg, 0.33 mmol, 2.5 equiv). The reaction mixture was stirred for 16 h and then H_2O was added. The mixture was poured into a separatory funnel where the layers were separated. The aqueous layer was extracted three times with DCM, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, concentrated and purified by flash chromatography (16 cm of height of silica gel, *n*-hexane/EtOAc 70/30) to yield aldol ***syn*-9b** (15 mg, 70%) as a colorless oil. R_F: 0.43 (*n*-hexane/EtOAc 60/40 two times); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 1.00 (t, J = 7.4 Hz, 3H, H_6), 1.15 (d, J = 6.4 Hz, 3H, $H_{2'}$), 2.06-2.12 (m, 2H, H_5), 2.59 (br s, 1H, OH), 2.94 (dd, J = 9.2, 5.2 Hz, 1H, H_2), 3.70 (s, 3H, CO_2Me), 4.00-4.05 (m, 1H, $H_{1'}$), 5.51 (dd, J = 15.2, 9.4 Hz, 1H, H_3), 5.70 (dt, J = 15.2, 6.4 Hz, 1H, H_4); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 13.6 (q, C_6), 20.1 (q, $C_{2'}$), 25.8 (t, C_5), 52.0 (q, $CO_2\underline{Me}$), 56.4 (d, C_2), 67.9 (d, $C_{1'}$), 122.3 (d, C_3), 139.0 (d, C_4), 174.3 (s, C_1); HRMS: calcd for $C_9H_{16}O_3Na$ [$(M + Na)^+$] 195.0997, found 195.0997.

General procedure for the synthesis of the 4-halo-2,3,4,5,6-pentasubstituted THPs 10. To a solution of the aldol and the aldehyde R^3CHO (1.5 equiv) in DCM (0.1 M) were sequentially added, under Ar atmosphere, TMSCl (1 equiv) and $Fe(acac)_3$ (0.1 equiv). Once TLC analysis revealed full conversion of the starting material (less than 30 min), the reaction was quenched by adding H_2O and the mixture was poured into a separatory funnel where the layers were separated. The aqueous layer was extracted three times with DCM, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, concentrated and purified by flash chromatography.

Ethyl (2S,3R*,4S*,5R*,6R*)-4-chloro-5-ethyl-2,6-diisobutyltetrahydro-2H-pyran-3-carboxylate (**10a**)*. *syn*-Aldol **9a** (109 mg, 0.48 mmol) was submitted to the general procedure for the synthesis of the 4-halo-2,3,4,5,6-pentasubstituted THPs **10** and yielded, after purification by flash chromatography (28 cm of height of silica gel, *n*-hexane/EtOAc 98/2), THP **10a** (111 mg, 70%, >95:5 dr). Alternatively, a solution of *syn*-aldol **9a** (150 mg, 0.66 mmol) and *i*-BuCHO (0.11 mL, 0.99 mmol, 1.5 equiv) in DCM (6.6 mL, 0.1 M) was treated with $FeCl_3$ (110 mg, 0.66 mmol, 1 equiv) and stirred for 30 min. Then, H_2O (10 mL) was added and the aqueous layer was extracted with DCM (3 x10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified as described above to yield title compound **10a** (103 mg, 47%, >95:5 dr) and undesired rearranged by-product **11** (11 mg, 7%). 4-chloro-THP **10a** was isolated as a white solid and its description is given below. R_F: 0.51 (*n*-hexane/EtOAc 98/2); mp56-60 ºC (from DCM/*n*-hexane); ^{1}H-NMR (400 MHz, δ, $CDCl_3$): 0.81-0.91 (m, 15H, 5xCH_3), 0.98-1.04 (m, 1H, $H_{1'}$), 1.27 (t, J = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.31-1.42 (m, 2H, $H_{1'''}$), 1.44-1.62 (m, 3H, H_5, 1x$H_{1'}$, 1x$H_{1''}$), 1.72-1.92 (m, 3H, 1x$H_{1''}$, $H_{2'}$, $H_{2'''}$), 2.56 (dd, J = 10.3, 10.3 Hz, 1H, H_3), 3.28 (td, J = 10.2, 2.4 Hz, 1H, H_6), 3.41 (td, J = 10.1, 1.9 Hz, 1H, H_2), 4.13-4.27 (m, 3H, H_4,

$CO_2C\underline{H}_2CH_3$); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 8.7 (q, $C_{2''}$), 14.4 (q, $CO_2CH_2\underline{C}H_3$), 20.0 (t, $C_{1''}$), 21.0 (q, $CH(\underline{C}H_3)_2$), 21.1 (q, $CH(\underline{C}H_3)_2$), 23.8 (q, $CH(\underline{C}H_3)_2$), 24.1 (q, $CH(\underline{C}H_3)_2$), 24.17 (d, $\underline{C}H(CH_3)_2$), 24.22 (d, $\underline{C}H(CH_3)_2$), 42.2 (t, $C_{1'''}$), 43.0 (t, $C_{1'}$), 48.6 (d, C_5), 59.4 (d, C_3), 61.1 (t, $CO_2\underline{C}H_2CH_3$), 62.4 (d, C_4), 76.3 (d, C_2), 77.1 (d, C_6), 171.7 (s, $\underline{C}O_2CH_2CH_3$); HRMS: calcd for $C_{18}H_{33}ClO_3Na$ [$(M + Na)^+$] 357.1986, found 357.1993.

Ethyl (2S,3S*,4S*,5R*,6R*)-4-chloro-5-ethyl-2,6-diisobutyltetrahydro-2H-pyran-3-carboxylate (**10b**)*. *anti*-**9a** (98 mg, 0.43 mmol) was submitted to the general procedure for the synthesis of the 4-halo-2,3,4,5,6-pentasubstituted THPs **10** and yielded, after a reaction time of 21 h and purification by flash chromatography (28 cm of height of silica gel, *n*-hexane/EtOAc 99/1), title compound **10b** (28 mg, 20%, >95:5 dr) and undesired lactone **12** (48 mg, 62%) as result of the 2-oxonia-Cope rearrangement. 4-chloro-THP **10b** was isolated as a white solid and its description is given below. R_F: 0.71 (*n*-hexane/EtOAc 90/10); mp 38-44 ºC (from DCM/*n*-hexane); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.83-0.92 (m, 15H, 5xCH_3), 1.19-1.25 (m, 1H, $H_{1'}$), 1.28 (t, J = 7.0 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.30-1.35 (m, 1H, $H_{1'''}$), 1.43-1.48 (m, 1H, 1x$H_{1'}$), 1.53-1.59 (m, 2H, 1x$H_{1''}$, 1x$H_{1'''}$), 1.67-1.73 (m, 1H, 1x$H_{1''}$), 1.79-1.86 (m, 1H, $H_{2'}$), 1.89-1.96 (m, 1H, $H_{2'''}$), 2.42 (ddt, J = 11.2, 11.2, 3.7 Hz, 1H, H_5), 2.97 (dd, J = 5.3, 2.7 Hz, 1H, H_3), 3.20 (td, J = 10.3, 1.9 Hz, 1H, H_6), 3.49 (dt, J = 9.9, 3.3 Hz, 1H, H_2), 4.09 (dd, J = 11.5, 5.5 Hz, 1H, H_4), 4.15-4.26 (m, 2H, $CO_2C\underline{H}_2CH_3$); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 8.7 (q, $C_{2''}$), 14.5 (q, $CO_2CH_2\underline{C}H_3$), 20.2 (t, $C_{1''}$), 21.1 (q, $CH(\underline{C}H_3)_2$), 21.7 (q, $CH(\underline{C}H_3)_2$), 23.4 (q, $CH(\underline{C}H_3)_2$), 24.0 (q, $CH(\underline{C}H_3)_2$), 24.1 (d, $\underline{C}H(CH_3)_2$), 24.5 (d, $\underline{C}H(CH_3)_2$), 42.1 (t, $C_{1'''}$), 42.5 (t, $C_{1'}$), 43.4 (d, C_5), 53.1 (d, C_3), 61.5 (t, $CO_2\underline{C}H_2CH_3$), 61.4 (d, C_4), 75.5 (d, C_2), 78.2 (d, C_6), 169.9 (s, $\underline{C}O_2CH_2CH_3$); HRMS: calcd for $C_{18}H_{33}ClO_3Na$ [$(M + Na)^+$] 357.1986, found 357.1986.

Methyl (2S,3R*,4S*,5R*,6R*)-6-butyl-4-chloro-5-ethyl-2-methyltetrahydro-2H-pyran-3-carboxylate (**10c**) and methyl (2S*,3R*,4S*,5R*,6R*)-2,6-dibutyl-4-chloro-5-ethyltetrahydro-2H-pyran-3-carboxylate (**10d**)*. *syn*-Aldol **9b** (53 mg, 0.31 mmol) was submitted to the general procedure for the synthesis of the 4-halo-2,3,4,5,6-pentasubstituted THPs **10** and yielded, after purification by flash chromatography (28 cm of height of silica gel, *n*-hexane/EtOAc 98/2), undesired THP **10d** (6 mg, 16%, >95:5 dr) and expected THP **10c** (17 mg, 20%, >95:5 dr), both as colorless oils. **10c**: R_F: 0.29 (*n*-hexane/EtOAc 95/5); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.87 (t, J = 7.5 Hz, 3H, $H_{2''}$), 0.90 (t, J = 7.0 Hz, 3H, $H_{4'''}$), 1.18 (d, J = 6.1 Hz, 3H, $H_{1'}$), 1.25-1.36 (m, 3H, 1x$H_{2'''}$, $H_{3'''}$), 1.38-1.44 (m, 1H, $H_{1'''}$), 1.45-1.50 (m, 1H, $H_{2'''}$), 1.53-1.57 (m, 1H, H_5), 1.57-1.62 (m, 1H, $H_{1''}$), 1.63-1.68 (m, 1H, $H_{1'''}$), 1.76-1.83 (m, 1H, $H_{1''}$), 2.58 (dd, J = J = 10.1, 10.1 Hz, 1H, H_3), 3.25-3.28 (m, 1H, H_6), 3.49 (dq, J = 9.8, 6.2 Hz, 1H, H_2), 3.75 (s, 3H, CO_2Me), 4.20 (dd, J = 11.0, 11.0 Hz, 1H, H_4); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 8.9 (q, $C_{2''}$), 14.2 (q, $C_{4'''}$), 20.02 (q, $C_{1'}$), 20.07 (t, $C_{1''}$), 22.8 (t, $C_{3'''}$), 27.6 (t, $C_{2'''}$), 32.7 (t, $C_{1'''}$), 47.6 (d, C_5), 52.2 (q, CO_2Me), 60.1 (d, C_3), 62.1 (d, C_4), 74.4 (d, C_2), 79.1 (d, C_6), 172.2 (s, CO$_2$Me); HRMS: calcd for $C_{14}H_{25}O_3Na^{37}Cl$ [(M + Na)$^+$] 301.1360, found 301.1362. **10d**: R_F: 0.34 (*n*-hexane/EtOAc 95/5); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.871 (t, J = 7.6 Hz, 3H, $H_{2''}$), 0.874 (t, J = 7.2 Hz, 3H, $H_{4'}$ or $H_{4'''}$), 0.91 (t, J = 7.1 Hz, 3H, $H_{4'}$ or $H_{4'''}$), 1.25-1.37 (m, 7H, 1x$H_{2'}$, 2x$H_{3'}$, 2x$H_{2'''}$, 2x$H_{3'''}$), 1.38-1.44 (m, 1H, $H_{1'''}$), 1.45-1.52 (m, 3H, 2x$H_{1'}$, 1x$H_{2'}$), 1.52-1.55 (m, 1H, H_5), 1.58-1.62 (m, 1H, $H_{1''}$), 1.64-1.69 (m, 1H, $H_{1'''}$), 1.75-1.82 (m, 1H, $H_{1''}$), 2.63 (dd, J = 10.2, 10.2 Hz, 1H, H_3), 3.22 (td, J = 9.6, 2.5 Hz, 1H, H_6), 3.33 (td, J = 9.4, 2.6 Hz, 1H, H_2), 3.75 (s, 3H, CO_2Me), 4.21 (dd, J = 11.0, 11.0 Hz, 1H, H_4); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 8.9 (q, $C_{2''}$), 14.1 (q, $C_{4'}$ or $C_{4'''}$), 14.2 (q, $C_{4'}$ or $C_{4'''}$), 20.1 (t, C1''), 22.5 (t, $C_{3'}$ or $C_{3'''}$), 22.6 (t, $C_{3'}$ or $C_{3'''}$), 27.5 (t, $C_{2'}$ or $C_{2'''}$), 27.7 (t, $C_{2'}$ or $C_{2'''}$), 32.7 (t, $C_{1'''}$), 33.8 (t, $C_{1'}$),

48.2 (d, C_5), 52.2 (q, $CO_2\underline{Me}$), 59.0 (d, C_3), 62.5 (d, C_4), 78.0 (d, C_2), 79.0 (d, C_6), 172.4 (s, $\underline{C}O_2Me$); HRMS: calcd for $C_{17}H_{31}O_3Na^{35}Cl$ [$(M + Na)^+$] 341.1859, found 341.1865.

Ethyl (4*S,5*R**,*E*)-4-ethyl-5-hydroxy-7-methyloct-2-enoate (11)**. This undesired by-products was obtained during the $FeCl_3$-mediated synthesis of previously described 4-chloro-THP **10a**, see synthetic procedure there. **11** (11 mg, 7%) was obtained as a colorless oil and its description is given below. R_F: 0.17 (*n*-hexane/EtOAc 90/10); ^{1}H-NMR (400 MHz, δ, $CDCl_3$): 0.88 (t, J = 7.7 Hz, 3H, $H_{2'}$), 0.91 (d, J = 6.5 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.92 (d, J = 6.6 Hz, 3H, $CH(C\underline{H}_3)_2$), 1.17-1.25 (m, 1H, H_6), 1.30 (t, J = 7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.34-1.40 (m, 1H, H_6), 1.43-1.53 (m, 1H, $H_{1'}$), 1.56-1.66 (m, 1H, $H_{1'}$), 1.71-1.82 (m, 1H, H_7), 2.02-2.09 (m, 1H, H_4), 3.70-3.74 (m, 1H, H_5), 4.20 (q, J = 7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 5.85 (d, J = 15.8 Hz, 1H, H_2), 6.85 (d, J = 15.7, 9.7 Hz, 1H, H_3); ^{13}C-NMR (100 MHz, δ, $CDCl_3$): 12.1 (q, $C_{2'}$), 14.4 (q, $CO_2CH_2\underline{C}H_3$), 22.0 (q, $CH(\underline{C}H_3)_2$), 23.7 (q, $CH(\underline{C}H_3)_2$), 23.9 (t, $C_{1'}$), 24.7 (d, C_7), 44.6 (t, C_6), 51.1 (d, C_4), 60.5 (t, $CO_2\underline{C}H_2CH_3$), 71.7 (d, C_5), 123.9 (d, C_2), 149.0 (d, C_3), 166.5 (s, $\underline{C}O_2CH_2CH_3$); HRMS: calcd for $C_{13}H_{24}O_3Na$ [$(M + Na)^+$] 251.1623, found 251.1624.

(5*R,6*S**)-5-Ethyl-6-isobutyl-5,6-dihydro-2*H*-pyran-2-one (12)**. This undesired by-products was obtained during the synthesis of previously described 4-chloro-THP **10b**, see synthetic procedure there. **12** (48 mg, 62%) was obtained as a colorless oil and its description is given below. R_F: 0.27 (*n*-hexane/EtOAc 90/10); ^{1}H-NMR (400 MHz, δ, $CDCl_3$): 0.90 (d, J = 6.4 Hz, 3H, $CH_2CH(C\underline{H}_3)_2$), 0.91 (d, J = 6.6 Hz, 3H, $CH_2CH(C\underline{H}_3)_2$), 0.96 (t, J = 7.4 Hz, 3H, $CH_2\underline{C}H_3$), 1.32-1.39 (m, 1H, $C\underline{H}_2CH(CH_3)_2$), 1.41-1.50 (m, 1H, $C\underline{H}_2CH_3$), 1.57-1.65 (m, 1H, $C\underline{H}_2CH_3$), 1.67-1.75 (m, 1H, $C\underline{H}_2CH(CH_3)_2$), 1.86-1.97 (m, 1H, $CH_2C\underline{H}(CH_3)_2$), 2.16-2.22 (m, 1H, H_5), 4.28 (ddd, J = 10.3, 7.4, 4.4 Hz, 1H, H_6), 5.95 (dd, J = 9.9, 1.9 Hz, 1H, H_3), 6.75 (dd, J = 9.8, 3.5 Hz, 1H, H_4); ^{13}C-NMR (100 MHz, δ, $CDCl_3$): 10.6 (q, $CH_2\underline{C}H_3$), 21.6 (q,

$CH_2CH(C\underline{H}_3)_2$), 23.5 (q, $CH_2CH(C\underline{H}_3)_2$), 24.1 (d, $CH_2C\underline{H}(CH_3)_2$), 24.3 (t, $\underline{C}H_2CH_3$), 39.9 (d, C_5), 42.5 (t, $\underline{C}H_2CH(CH_3)_2$), 79.8 (d, C_6), 120.6 (d, C_3), 149.1 (d, C_4), 163.9 (s, C_2); MS (EI) m/z (relative intensity): 182 $(M)^+$ (1), 168 $(M + 1 - Me)^+$ (1), 125 (M – *i*-Bu)$^+$ (47), 96 (100); HRMS: calcd for $C_{11}H_{18}O_2$ [$(M)^+$] 182.1307, found 182.1300.

Methyl (2*S,3*R**,5*S**,6*R**)-5-ethyl-4-hydroxy-2,6-dimethyltetrahydro-2*H*-pyran-3-carboxylate (13)**. *syn*-Aldol **9b** (37 mg, 0.22 mmol) was submitted to the general procedure for the synthesis of the bicycles **5** (two-steps EAP). Once completed the reaction, ^{1}H-NMR analysis of the crude revealed a 1/1 mixture of the epimers at C_4 of THP **13**. After purification by flash chromatography (21 cm of height of silica gel, *n*-hexane/EtOAc 95/5), that inseparable mixture of the isomers of **13** (6 mg, 12%, 50:50 dr) was isolated. The mixture decomposed after 1 month, in spite of have been stored under Ar at –18 ºC. Appearance: colorless oil; R_F: 0.49 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (400 MHz, δ, $CDCl_3$): 0.94 (t, J = 7.6 Hz, 3H, $H_{2''}$), 1.20 (d, J = 6.1 Hz, 3H, $H_{1'}$), 1.26 (d, J = 5.8 Hz, 3H, $H_{1'''}$), 1.40-1.55 (m, 2H, H_5, $H_{1''}$), 1.61-1.71 (m, 1H, $H_{1''}$), 2.46-2.53 (m, 1H, H_3), 3.31-3.38 (m, 1H, H_6), 3.49-3.57 (m, 1H, H_2), 3.75 (s, 3H, $CO_2\underline{Me}$), 4.67 (dd, J = 10.3 Hz, 0.5H, H_4), 4.80 (dd, J = 10.2 Hz, 0.5H, H_4); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 10.0 (q, $C_{2''}$), 19.2 (q, $C_{1'''}$), 19.79 (t, $C_{1''}$), 19.83 (q, $C_{1'}$), 47.7 and 47.8 (d, C_5), 52.2 (q, $CO_2\underline{Me}$), 56.5 and 56.7 (d, C_3), 72.6 and 72.7 (d, C_2), 74.4 and 74.5 (d, C_6), 92.4 and 93.9 (d, C_4), 172.3 (s, $\underline{C}O_2Me$); HRMS: calcd for $C_{11}H_{20}O_4Na$ [$(M + Na)^+$] 239.1259, found 239.1257.

(2*S,5*S**,6*R**)-5-Ethyl-*N*-(2-hydroxyethyl)-2,6-diisobutyl-5,6-dihydro-2*H*-pyran-3-carboxamide (14)**. A 1 M solution of KHMDS in THF (0.76 mL, 0.76 mmol, 1.5 equiv) was added, at –78 ºC and under Ar atmosphere, dropwise to a stirred solution of bicycle **5a** (179 mg, 0.50 mmol) in THF (2.8 mL, 0.2 M). The reaction mixture was stirred at –78 ºC for 2 h, until TLC analysis revealed full conversion of the starting

material. Then, the cold bath was removed, the reaction was quenched with a saturated NH_4Cl aqueous solution (5 mL) and the mixture was poured into a separatory funnel with 5 mL of DCM. The layers were separated, the aqueous layer was extracted with DCM (3 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (21 cm of height of silica gel, *n*-hexane/EtOAc 30/70) to yield title compound **14** (73 mg, 47%) as a colorless oil. Product **14** revealed properly with oleum and with a phosphomolybdic acid, although it did not reveal with ninhydrin, vanillin or anisaldehyde. R_F: 0.35 (*n*-hexane/EtOAc 20/80); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.85-0.94 (m, 15H, 2x($C\underline{H}_3$)$_2$CHCH$_2$, 3x$H_{2''}$), 1.12-1.23 (m, 1H, $H_{1''}$), 1.29-1.43 (m, 4H, 2x$(CH_3)_2CHC\underline{H}_2$), 1.44-1.55 (m, 1H, $H_{1''}$), 1.84-1.97 (m, 3H, H_5, 2x$(CH_3)_2C\underline{H}CH_2$), 2.95 (br s, 1H, OH), 3.17 (td, J = 9.4, 3.0 Hz, 1H, H_6), 3.46 (t, J = 5.6 Hz, 2H, N$C\underline{H}_2CH_2OH$), 3.74 (t, J = 4.9 Hz, 2H, $NCH_2C\underline{H}_2OH$), 4.39-4.44 (m, 1H, H_2), 6.16 (br s, 1H, H_4), 6.24 (t, J = 5.2 Hz, 1H, NH); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 10.4 (q, $C_{2''}$), 21.0 (q, ($\underline{C}H_3$)$_2$CHCH$_2$), 21.4 (q, ($\underline{C}H_3$)$_2$CHCH$_2$), 23.4 (t, $C_{1''}$), 23.9 (q, 2C, 2x($\underline{C}H_3$)$_2$CHCH$_2$), 24.4 (d, $(CH_3)_2\underline{C}HCH_2$), 24.6 (d, $(CH_3)_2\underline{C}HCH_2$), 41.5 (d, C_5), 42.0 (t, $(CH_3)_2CH\underline{C}H_2$), 42.2 (t, $(CH_3)_2CH\underline{C}H_2$), 42.3 (t, N$\underline{C}H_2CH_2OH$), 62.1 (t, N$\underline{C}H_2CH_2OH$), 72.7 (d, C_2), 75.1 (d, C_6), 132.6 (d, C_4), 139.7 (s, C_3), 170.3 (s, $C_3\underline{C}$(O)N); MS (EI) m/z (relative intensity): 312 $(M + 1)^+$ (8), 311 $(M)^+$ (23), 294 $(M - OH)^+$ (5), 282 $(M - Et)^+$ (7), 266 $(M - CH_2CH_2OH)^+$ (4), 254 (M – *i*-Bu)$^+$ (28), 236 $(M - i\text{-}Bu - H_2O)^+$ (8), 225 $(M - Et - i\text{-}Bu)^+$ (30), 197 $(M - 2\ i\text{-}Bu)^+$ (2), 182 $(M + 1 - i\text{-}Bu - Me - NHCH_2CH_2OH)^+$ (100), 168 $(M - 2\ i\text{-}Bu - Et)^+$ (5); HRMS: calcd for $C_{18}H_{33}NO_3$ [$(M)^+$] 311.2460, found 311.2445.

(2*S,3*R**,4*S**,5*S**,6*R**)-5-Ethyl-4-hydroxy-*N*-(2-hydroxyethyl)-2,6-diisobutyltetrahydro-2*H*-pyran-3-carboxamide (15)**. To a solution of bicycle **5a** (162 mg, 0.46 mmol) in MeOH (3.3 mL, 0.14 M) was added $MeSO_3H$ (0.02 mL,

0.32 mmol, 0.7 equiv) and the mixture was heated at 60 ºC for 8 h. After that, it was allowed to warm to rt and $Ba(OH)_2 \cdot 8H_2O$ (432 mg, 1.37 mmol, 3 equiv) was added. Then, the mixture was heated again at 60 ºC for an extra 2 h and next was cooled to rt. A 1 M aqueous solution of HCl (5 mL) was added, and the aqueous layer was extracted with Et2O (3 x 5 mL), the combined organic layers were washed with brine (15 mL), dried over MgSO4, filtered, concentrated and purified by flash chromatography (21 cm of height of silica gel, EtOAc) to yield title compound **15** (89 mg, 60%) as an amorphous white solid. R_F: 0.33 (DCM/MeOH 90/10), 0.51 (EtOAc/HOAc 95/5); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.85-0.93 (m, 15H, 5xMe), 1.10-1.16 (m, 1H, $(CH_3)_2CHC\underline{H}_2$), 1.21-1.27 (m, 2H, H_5, $(CH_3)_2CHC\underline{H}_2$), 1.29-1.39 (m, 1H, $(CH_3)_2CHC\underline{H}_2$), 1.37-1.46 (m, 1H, $(CH_3)_2CHC\underline{H}_2$), 1.49-1.56 (m, 1H, $H_{1''}$), 1.61-1.70 (m, 1H, $H_{1''}$), 1.83-1.93 (m, 2H, 2x$(CH_3)_2C\underline{H}CH_2$), 1.98 (dd, J = 9.6 Hz, 1H, H_3), 3.15-3.22 (m, 1H, $NC\underline{H}_2CH_2OH$), 3.27 (td, J = 10.2, 1.9 Hz, 1H, H_6), 3.40-3.56 (m, 2H, 2xOH), 3.52 (td, J = 10.1, 1.8 Hz, 1H, H_2), 3.60-3.74 (m, 2H, 1x$NC\underline{H}_2CH_2OH$, 1x$NCH_2C\underline{H}_2OH$), 3.76-3.82 (m, 1x$NCH_2C\underline{H}_2OH$), 3.89 (dd, J = 10.1, 10.1 Hz, 1H, H_4), 6.29 (br s, 1H, NH); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.5 (q, $C_{2''}$), 19.0 (t, $C_{1''}$), 21.1 (q, 2x$(\underline{C}H_3)_2CHCH_2$), 23.9 (q, $(\underline{C}H_3)_2CHCH_2$), 24.1 (q, $(\underline{C}H_3)_2CHCH_2$), 24.2 (d, $(CH_3)_2\underline{C}HCH_2$), 24.3 (d, $(CH_3)_2\underline{C}HCH_2$), 42.1 (t, $N\underline{C}H_2CH_2OH$), 42.3 (t, $(CH_3)_2CH\underline{C}H_2$), 42.9 (t, $(CH_3)_2CH\underline{C}H_2$), 48.3 (d, C_5), 59.5 (d, C_3), 61.4 (t, $NCH_2\underline{C}H_2OH$), 71.7 (d, C_4), 74.7 (d, C_2), 76.0 (d, C_6), 174.1 (s, $C_3\underline{C}ONH$); MS (EI) m/z (relative intensity): 330 $(M + 2)^+$ (1), 328 $(M)^+$ (1), 312 $(M - OH)^+$ (1), 311 $(M - H_2O)^+$ (2), 298 $(M - CH_2OH)^+$ (1), 272 $(M - i\text{-Bu})^+$ (8), 227 $(M - i\text{-Bu} - CH_2CH_2OH)^+$ (2), 216 $(M + 1 - 2\ i\text{-Bu})^+$ (100), 188 $(M + 2 - 2\ i\text{-Bu} - Et)^+$ (16); HRMS: calcd for $C_{18}H_{34}NO_4$ $[(M)^+]$ 328.2488, found 328.2497.

(2*S,3*S**,4*S**,5*R**,6*R**)-5-Ethyl-4-(((2-hydroxyethyl)carbamoyl)oxy)-2,6-diisobutyltetrahydro-2*H*-pyran-3-carboxylic acid (16)**. To an ice-cooled solution of bicycle **5a** (1.19 g, 3.36 mmol) in a 3/1 mixture of THF/H_2O (60 mL, 0.05 M) was added a 35% w/w aqueous solution of H_2O_2 (1.8 mL, 20.2 mmol, 6 equiv) and $LiOH{\cdot}H_2O$ (287 mg, 6.72 mmol, 2 equiv). The mixture was allowed to warm to rt and was stirred for 21 h, when an aliquot was taken, diluted with a small amount of EtOAc and treated with a few drops of a 5% HCl aqueous solution. TLC analysis of the treated aliquot revealed full conversion of the starting material. After that, the reaction mixture was cooled to 0 ºC and was quenched with a 1.5 M aqueous solution of Na_2SO_3 (60 mL). Then, the THF was evaporated in the rotavap and the remaining solution was diluted with H_2O (40 mL), washed with DCM (100 mL), acidified to pH = 1 with a 5% HCl aqueous solution and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (500 mL), dried over $MgSO_4$, filtered and concentrated. The tenth of the crude was separated and purified by flash chromatography (9 cm of height of silica gel, 100 mL of EtOAc and then EtOAc/MeOH 80/20) to yield title compound **16** (98 mg, which mathematically means a total yield of 79%) as an amorphous white solid. The non-purified crude was consumed in the synthesis of THP **17**. R_F: 0.24 (EtOAc), 0.38 (EtOAc/HOAc 95/5), 0.39 (EtOAc/MeOH 90/10), 0.54 (EtOAc/MeOH 80/20), 0.75 (DCM/MeOH 80/20); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.85-0.93 (m, 15H, 5xCH_3), 1.16-1.25 (m, 1H, 1x$(CH_3)_2CHC\underline{H}_2$), 1.26-1.35 (m, 1H, 1x$(CH_3)_2CHC\underline{H}_2$), 1.37-1.55 (m, 5H, H_5, 1x$H_{1'}$, 2x$H_{1''}$, 1x$H_{1'''}$), 1.83-1.95 (m, 2H, 2x$(CH_3)_2C\underline{H}CH_2$), 2.35 (dd, J = 10.2, 10.2 Hz, 1H, H_3), 3.08-3.16 (m, 1H, $NC\underline{H}_2CH_2OH$), 3.30-3.36 (m, 1H, H_6), 3.43-3.67 (m, 3H, H_2, 1x$NC\underline{H}_2CH_2OH$, 1x$NCH_2C\underline{H}_2OH$), 3.72-3.82 (m, 1H, $NCH_2C\underline{H}_2OH$), 5.15 (dd, J = 10.5, 10.5 Hz, 1H, H_4), 5.23-5.32 (m, 1H, NH); ^{1}H-NMR (500 MHz, δ, $(D_3C)_2CO$): 0.85-0.94 (m, 15H,

5xCH_3), 1.13-1.21 (m, 1H, $H_{1'}$), 1.29-1.34 (m, 1H, H_5), 1.35-1.40 (m, 2H, $H_{1'''}$), 1.42-1.52 (m, 3H, 1x$H_{1'}$, 2x $H_{1''}$), 1.85-1.97 (m, 2H, 2x$(CH_3)_2CHCH_2$), 2.25 (dd, J = 10.1, 10.1 Hz, 1H, H_3), 3.17-3.24 (m, 2H, NCH_2CH_2OH), 3.39 (td, J = 9.7, 4.0 Hz, 1H, H_6), 3.50-3.60 (m, 3H, H_2, NCH_2CH_2OH), 5.16 (dd, J = 10.5, 10.5 Hz, 1H, H_4), 6.19 (br s, 1H, NH); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.7 (q, $C_{2''}$), 19.4 (t, $C_{1''}$), 21.3 (q, 2C, 2x$(CH_3)_2CHCH_2$), 23.8 (q, $(CH_3)_2CHCH_2$), 24.1 (q, $(CH_3)_2CHCH_2$), 24.4 (d, $(CH_3)_2CHCH_2$), 24.5 (d, $(CH_3)_2CHCH_2$), 42.1 (t, $(CH_3)_2CHCH_2$), 43.2 (t, $(CH_3)_2CHCH_2$), 43.6 (t, NCH_2CH_2OH), 46.4 (d, C_5), 56.2 (d, C_3), 61.7 (t, NCH_2CH_2OH), 75.1 (d, C_4), 76.4 (d, C_6), 76.6 (d, C_2), 157.7 (s, $OC(O)NH$), 175.5 (s, CO_2H); ^{13}C-NMR (125 MHz, δ, $(D_3C)_2CO$): 9.5 (q, $C_{2''}$), 19.5 (t, $C_{1''}$), 21.4 (q, $(CH_3)_2CHCH_2$), 21.5 (q, $(CH_3)_2CHCH_2$), 24.1 (q, $(CH_3)_2CHCH_2$), 24.3 (q, $(CH_3)_2CHCH_2$), 24.90 (d, $(CH_3)_2CHCH_2$), 25.01 (d, $(CH_3)_2CHCH_2$), 42.7 (t, $C_{1'''}$), 43.9 (t, $C_{1'}$), 44.3 (t, NCH_2CH_2OH), 47.5 (d, C_5), 56.5 (d, C_3), 61.9 (t, NCH_2CH_2OH), 74.0 (d, C_4), 75.3 (d, C_2), 76.4 (d, C_6), 157.2 (s, $OC(O)NH$), 173.2 (s, CO_2H); MS (EI) m/z (relative intensity): 344 $(M - Et)^+$ (1), 343 $(M - 1 - Et)^+$ (4), 316 $(M - i\text{-Bu})^+$ (4), 287 $(M - i\text{-Bu} - Et)^+$ (4), 269 $(M - \text{carbamate})^+$ (34), 229 $(M - 1 - 2\ i\text{-Bu} - Et)^+$ (13), 223 $(M - 1 - \text{carbamate} - CO_2H)^+$ (20), 211 $(M - 1 - i\text{-Bu} - \text{carbamate})^+$ (100), 155 $(M - \text{carbamate} - 2\ i\text{-Bu})^+$ (27), 126 $(M - 2\ i\text{-Bu} - \text{carbamate} - 2\ Et)^+$ (28), 110 $(M - 2\ i\text{-Bu} - \text{carbamate} - CO_2H)^+$ (17); HRMS: calcd for $C_{17}H_{29}NO_6$ $[(M - 1 - Et)^+]$ 343.1995, found 343.1987; HRMS: calcd for $C_{12}H_{19}O_3$ $[(M + 1 - i\text{-Bu} - \text{carbamate})^+]$ 211.1334, found 211.1339.

(2*S,3*R**,4*S**,5*S**,6*R**)-5-Ethyl-4-hydroxy-2,6-diisobutyltetrahydro-2*H*-pyran-3-carboxylic acid (17)**. THP **16** (95 mg, 0.26 mmol) was dissolved in a 3/1/1 mixture of THF/MeOH/H_2O (3.5 mL, 0.07 M) and $LiOH \cdot H_2O$ (164 mg, 3.83 mmol, 15 equiv) was added. The reaction mixture was heated at 80 ºC for 24 h. After that, an aliquot was

taken, diluted with a small amount of EtOAc and treated with a few drops of a 5% HCl aqueous solution. TLC analysis of the treated aliquot revealed full conversion of the starting material. The organic solvents were removed in the rotavap, and then the aqueous mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (15 mL), and when the huge emulsion disappeared, the organic layer was separated, dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (14 cm of height of silica gel, 60 mL of EtOAc/MeOH 98/2 followed by 60 mL of EtOAc/MeOH 90/10 and 60 mL of EtOAc/MeOH 80/20) to yield title compound **17** (52 mg, 70%) as an amorphous white solid. A similar yield was obtained when the reaction was performed with non-purified THP **16** as starting material. THP **17** shows decreasing solubility in deuterated solvents according to the following order: DMSO-d_6 >> acetone-d_6 > MeOD >> $CDCl_3$ > C_6D_6 >>> D_2O (totally insoluble). R_F: 0.28 (EtOAc), 0.46 (EtOAc/MeOH 95/5), 0.53 (EtOAc/HOAc 97.5/2.5), 0.69 (EtOAc/HOAc 95/5); ^{1}H-NMR (500 MHz, δ, $(D_3C)_2CO$): 0.84-0.93 (m, 15H, 5xCH_3), 1.12-1.21 (m, 2H, H_5, 1x$(CH_3)_2CHC\underline{H}_2$), 1.34-1.39 (m, 2H, $(CH_3)_2CHC\underline{H}_2$), 1.44-1.49 (m, 1H, $(CH_3)_2CHC\underline{H}_2$), 1.49-1.56 (m, 1H, $H_{1''}$), 1.69-1.79 (m, 1H, $H_{1''}$), 1.84-1.96 (m, 2H, $(CH_3)_2C\underline{H}CH_2$), 2.17 (dd, J = 10.0, 10.0 Hz, 1H, H_3), 3.25-3.31 (m, 1H, H_6), 3.42 (td, J = 10.2, 2.0 Hz, 1H, H_2), 3.79 (dd, J = 10.2, 10.2 Hz, 1H, H_4); ^{13}C-NMR (125 MHz, δ, $(D_3C)_2CO$): 9.8 (q, $C_{2''}$), 19.4 (t, $C_{1''}$), 21.4 (q, $(\underline{C}H_3)_2CHCH_2$), 21.5 (q, $(\underline{C}H_3)_2CHCH_2$), 24.2 (q, $(\underline{C}H_3)_2CHCH_2$), 24.4 (q, $(\underline{C}H_3)_2CHCH_2$), 24.92 (d, $(CH_3)_2\underline{C}HCH_2$), 24.94 (d, $(CH_3)_2\underline{C}HCH_2$), 43.0 (t, $(CH_3)_2CH\underline{C}H_2$), 44.1 (t, $(CH_3)_2CH\underline{C}H_2$), 49.4 (d, C_5), 59.1 (d, C_3), 72.4 (d, C_4), 75.5 (d, C_2), 76.7 (d, C_6), 174.7 (s, CO_2H); MS (EI) m/z (relative intensity): 268 $(M - H_2O)^+$ (18), 240 $(M - 1 - CO_2H)^+$ (2), 229 $(M - i\text{-Bu})^+$ (49), 211 $(M - i\text{-Bu} - H_2O)^+$ (28), 182 $(M - 2 - i\text{-Bu} - CO_2H)^+$

(13), 173 (M + 1 – 2 *i*-Bu)$^+$ (17); HRMS: calcd for $C_{16}H_{28}O_3$ [(M – H_2O)$^+$] 268.2038, found 268.2034.

(2*R,3*S**,4*S**,5*R**,6*S**)-3-Ethyl-5-(((2-hydroxyethyl)(methyl)amino)methyl)-2,6-diisobutyltetrahydro-2*H*-pyran-4-ol (18)**. To an ice-cooled 1 M solution of DIBAL-H in hexanes (4 mL, 4 mmol, 9 equiv) was dropwise added, under Ar atmosphere and for 7 min, a solution of bicycle **5a** (159 mg, 0.45 mmol) in Et_2O (4.5 mL, 0.1 M). 5 min after the addition, TLC analysis revealed that the reaction was completed. At 20 min, the mixture was diluted with Et_2O (20 mL) and a saturated Rochelle salt aqueous solution (5 mL) was added. The mixture was vigorously stirred for 1 h, until two clear phases were observed when the stirring was stopped. The layers were separated in a separatory funnel, the aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (16 cm of height of silica gel, DCM/MeOH 95/5) to yield title compound **18** (97 mg, 66%) as a yellowish oil. R_F: 0.24 (DCM/MeOH 95/5); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.79-0.90 (m, 15H, 5x(CH_3)), 1.15-1.20 (m, 1H, $H_{1'''}$), 1.25-1.32 (m, 2H, H_3, $H_{1'}$), 1.35-1.42 (m, 2H, $H_{1'}$, $H_{1'''}$), 1.43-1.49 (m, 1H, $H_{1''}$), 1.52-1.60 (m, 1H, H_5), 1.58-1.65 (m, 1H, $H_{1''}$), 1.80-1.92 (m, 2H, $H_{2'}$, $H_{2'''}$), 2.31 (s, 3H, C$\underline{H}_3$N), 2.40-2.47 (m, 2H, 1x $C_5C\underline{H}_2N$, 1x$NC\underline{H}_2CH_2OH$), 2.47 (dd, J = 12.6, 2.9 Hz, 1H, $C_5C\underline{H}_2N$), 2.67-2.72 (m, 1H, $NC\underline{H}_2CH_2OH$), 2.97 (td, J = 9.5, 1.8 Hz, 1H, H_6), 3.17 (td, J = 10.4, 1.9 Hz, 1H, H_2), 3.56 (dd, J = 9.7, 9.7 Hz, 1H, H_4), 3.64-3.74 (m, 2H, $NCH_2C\underline{H}_2OH$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.3 (q, $C_{2''}$), 18.5 (t, $C_{1''}$), 21.05 (q, ($\underline{C}H_3$)$_2$CHCH$_2$), 21.06 (q, ($\underline{C}H_3$)$_2$CHCH$_2$), 24.0 (q, ($\underline{C}H_3$)$_2$CHCH$_2$), 24.1 (d, 2C, 2x(CH_3)$_2\underline{C}$HCH$_2$), 24.2 (q, ($\underline{C}H_3$)$_2$CHCH$_2$), 42.1 (t, $C_{1'}$), 42.5 (t, $C_{1'''}$), 43.2 (q, $\underline{C}H_3N$), 45.2 (d, C_5), 48.4 (d, C_3), 59.6 (t, $NCH_2\underline{C}H_2OH$), 60.4 (t, $N\underline{C}H_2CH_2OH$), 61.2 (t, $C_5\underline{C}H_2N$), 74.6 (d, C_6), 75.9 (d, C_2), 77.2 (d, C_4); MS (EI) m/z (relative intensity): 330

$(M + 1)^+$ (1), 329 $(M)^+$ (1), 314 $(M - Me)^+$ (1), 298 $(M - CH_2OH)^+$ (14), 272 (M – *t*-Bu)$^+$ (1), 216 $(M + 1 - 2\ t\text{-Bu})^+$ (6), 186 $(M - 2\ t\text{-Bu} - Et)^+$ (1), 88 (100); HRMS: calcd for $C_{19}H_{39}NO_3$ $[(M)^+]$ 329.2930, found 329.2922.

(2*R,3*S**,4*S**,5*R**,6*S**)-3-Ethyl-5-(hydroxymethyl)-2,6-diisobutyltetrahydro-2*H*-pyran-4-ol (19)**. To a solution of bicycle **5a** (285 mg, 0.73 mmol) in THF (7 mL, 0.1 M) was dropwise added, at rt and under Ar atmosphere, a 1 M solution of DIBAL-H in hexanes (8 mL, 8 mmol, 11 equiv). Then, the reaction mixture was heated at 66 ºC for 19 h. Once TLC analysis revealed that the reaction was completed, it was cooled to rt, diluted with Et_2O (50 mL) and quenched with a saturated Rochelle salt aqueous solution (10 mL). The mixture was vigorously stirred for 1 h, and then was poured into a separatory funnel together with H_2O (40 mL). The layers were separated, the aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (35 cm of height of silica gel, *n*-hexane/EtOAc 75/25) to yield diol **19** (71 mg, 36%). Alternatively, carbamate **20** (65 mg, 0.18 mmol) was dissolved in a 1/1/1 mixture of THF/MeOH/H_2O (2.6 mL, 0.07 M) and $LiOH{\cdot}H_2O$ (78 mg, 1.85 mmol, 10 equiv) was added. It was heated at 80 ºC for 5 saturated NH_4Cl aqueous solution (5 mL) and the aqueous mixture was extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (14 cm of height of silica gel, *n*-hexane/EtOAc 60/40) to yield diol **19** (38 mg, 80%). Appearance: amorphous white solid. R_F: 0.25 (*n*-hexane/EtOAc 50/50), 0.40 (*n*-hexane/EtOAc 20/80); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.84 (d, J = 6.6 Hz, 3H, $(C\underline{H}_3)_2CHCH_2$), 0.86 (d, J = 6.4 Hz, 3H, $(C\underline{H}_3)_2CHCH_2$), 0.89 (t, J = 7.5 Hz, 3H, $H_{2''}$), 0.91 (d, J = 7.0 Hz, 3H, $(C\underline{H}_3)_2CHCH_2$), 0.92 (d, J = 7.0 Hz, 3H, $(C\underline{H}_3)_2CHCH_2$), 1.20-1.25 (m, 1H, $(CH_3)_2CHC\underline{H}_2$), 1.28-1.33 (m, 2H, H_3, 1x$(CH_3)_2CHC\underline{H}_2$), 1.39-1.56

(m, 4H, H_5, 1x$H_{1''}$, 2x$(CH_3)_2CHC\underline{H}_2$), 1.62-1.70 (m, 1H, $H_{1''}$), 1.86-1.96 (m, 2H, 2x$(CH_3)_2C\underline{H}CH_2$), 2.50 (br s, 1H, OH), 2.84 (br s, 1H, OH), 3.11 (td, J = 10.4, 2.8 Hz, 1H, H_6), 3.18 (td, J = 10.4, 2.5 Hz, 1H, H_2), 3.64 (dd, J = 10.6, 8.1 Hz, 1H, 1x$C\underline{H}_2OH$), 3.70 (dd, J = 9.9, 9.9 Hz, 1H, H_4), 3.96 (dd, J = 10.6, 3.4 Hz, 1H, 1x$C\underline{H}_2OH$); ^{1}H-NMR (600 MHz, δ, C_6D_6): 0.88-0.95 (m, 15H, 3x$H_{2''}$, 4x$(C\underline{H}_3)_2CHCH_2$), 1.09-1.15 (m, 1H, $H_{1'''}$), 1.27-1.35 (m, 2H, H_3, $H_{1'''}$), 1.39-1.51 (m, 4H, H_5, 2x$H_{1'}$, 1x$H_{2'}$), 1.60 (br s, 1H, CH_2OH), 1.69-1.76 (m, 1H, $H_{1''}$), 2.02-2.14 (m, 2H, $H_{2'}$, $H_{2'''}$), 2.66 (br s, 1H, C_4OH), 2.95-3.01 (m, 1H, H_6), 3.07-3.12 (m, 1H, H_2), 3.27-3.32 (m, 1H, 1x$C_5C\underline{H}_2OH$), 3.51-3.56 (m, 1H, H_4), 3.60-3.65 (m, 1H, 1x$C_5C\underline{H}_2OH$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.4 (q, $C_{2''}$), 18.8 (t, $C_{1''}$), 21.1 (q, 2C, $(\underline{C}H_3)_2CHCH_2$), 24.1 (d, $(CH_3)_2\underline{C}HCH_2$), 24.15 (q, 2C, $(\underline{C}H_3)_2CHCH_2$), 24.19 (d, $(CH_3)_2\underline{C}HCH_2$), 42.2 (t, $(CH_3)_2CH\underline{C}H_2$), 42.7 (t, $(CH_3)_2CH\underline{C}H_2$), 49.1 (d, C_3), 50.6 (d, C_5), 63.9 (t, $\underline{C}H_2OH$), 74.0 (d, C_6), 74.5 (d, C_4), 75.8 (d, C_2); HRMS: calcd for $C_{16}H_{32}O_3Na$ [$(M + Na)^+$] 295.2249, found 295.2251.

(2*R,3*R**,4*S**,5*S**,6*S**)-3-Ethyl-5-(hydroxymethyl)-2,6-diisobutyltetrahydro-2*H*-pyran-4-yl (2-hydroxyethyl)carbamate (20)**. Bicycle **5a** (175 mg, 0.49 mmol) was dissolved in a 4/1 mixture of THF/H_2O (5 mL, 0.1 M), the solution was cooled to 0 ºC and $NaBH_4$ (75 mg, 1.96 mmol, 4 equiv) was added. Then, the reaction mixture was allowed to warm to rt and was stirred for 16 h. After that, it was quenched with a saturated Rochelle salt aqueous solution (5 mL). The mixture was vigorously stirred for 16 h, and then was poured into a separatory funnel together with EtOAc (10 mL). The layers were separated, the aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (12 cm of height of silica gel, *n*-hexane/EtOAc 30/70) to yield compound **20** (128 mg, 70%) as an amorphous white solid.[84] R_F: 0.29 (EtOAc/MeOH 80/20); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.85 (t,

J = 7.5 Hz, 3H, $H_{2''}$), 0.87 (d, J = 6.6 Hz, 3H, $(C\underline{H}_3)_2CHCH_2$), 0.89 (d, J = 6.5 Hz, 3H, $(C\underline{H}_3)_2CHCH_2$), 0.92 (d, J = 6.8 Hz, 6H, $(C\underline{H}_3)_2CHCH_2$), 1.27-1.34 (m, 2H, H_5, $H_{1'''}$), 1.38-1.52 (m, 6H, H_3, $2xH_{1'}$, $2xH_{1''}$, $H_{1'''}$), 1.87-1.98 (m, 2H, $(CH_3)_2C\underline{H}CH_2$), 3.26 (td, J = 10.2, 2.1 Hz, 1H, H_2), 3.33-3.44 (m, 2H, $NC\underline{H}_2CH_2OH$), 3.51 (td, J = 10.0, 2.9 Hz, 1H, H_6), 3.54 (dd, J = 12.9, 2.5 Hz, 1H, $C_5C\underline{H}_2OH$), 3.61-3.65 (m, 1H, $C_5C\underline{H}_2OH$), 3.74 (t, J = 5.0 Hz, 2H, $NCH_2C\underline{H}_2OH$), 4.92 (dd, J = 10.5, 10.5 Hz, 1H, H_4), 5.25 (t, J = 5.7 Hz, 1H, NH); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.4 (q, $C_{2''}$), 19.7 (t, $C_{1''}$), 21.05 (q, $(\underline{C}H_3)_2CHCH_2$), 21.08 (q, $(\underline{C}H_3)_2CHCH_2$), 24.1 (q, $(\underline{C}H_3)_2CHCH_2$), 24.16 (d, $(CH_3)_2\underline{C}HCH_2$), 24.17 (q, $(\underline{C}H_3)_2CHCH_2$), 24.3 (d, $(CH_3)_2\underline{C}HCH_2$), 41.9 (t, $(CH_3)_2CH\underline{C}H_2$), 42.2 (t, $(CH_3)_2CH\underline{C}H_2$), 43.6 (t, $N\underline{C}H_2CH_2OH$), 46.8 (d, C_3), 50.6 (d, C_5), 58.1 (t, $C_5\underline{C}H_2OH$), 62.3 (t, $NCH_2\underline{C}H_2OH$), 73.1 (d, C_4), 73.8 (d, C_6), 75.7 (d, C_2), 158.8 (s, $O\underline{C}(O)N$); MS (EI) m/z (relative intensity): 302 $(M - i\text{-Bu})^+$ (3), 254 $(M - 1 - OC(O)NHCH_2CH_2OH)^+$ (5), 223 $(M - 1 - \text{carbamate} - CH_2OH)^+$ (31), 197 $(M - 1 - i\text{-Bu} - \text{carbamate})^+$ (100), 168 $(M + 1 - i\text{-Bu} - \text{carbamate} - CH_2OH)^+$ (41), 141 $(M - 2\ i\text{-Bu} - \text{carbamate})^+$ (9), 111 $(M + 1 - 2\ i\text{-Bu} - \text{carbamate} - CH_2OH)^+$ (12); HRMS: calcd for $C_{15}H_{28}NO_5$ $[(M - i\text{-Bu})^+]$ 302.1967, found 302.1961.

Synthesis of the 3-(*N*-acyl oxazolidin-2-one)-THPs 21.

*(R)-4-Benzyl-3-((2S,3R,4S,5S,6R)-5-ethyl-4-hydroxy-2,6-dimethyltetrahydro-2H-pyran-3-carbonyl)oxazolidin-2-one (**21a**)*. Aldol **2i** (26 mg, 83 μmol) and acetaldehyde (37 μL of a 3.3 M solution in DCM, 125 μmol, 1.5 equiv) were submitted to the general procedure for the synthesis of the bicycles **5** (two-steps EAP) and yielded, after purification by flash chromatography (18 cm of height of silica gel, *n*-hexane/EtOAc 70/30), title compound **21a** (3 mg, 9%, >95:5 dr) and previously described **5ag** (19 mg, 62%, >95:5 dr). Appearance: thick colorless oil; R_F: 0.43 (*n*-hexane/EtOAc 60/40); $[\alpha]^{25}_D$ –66.0 (*c* 0.6, $CHCl_3$); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.93 (t, J = 7.6 Hz, 3H,

$C_{5'}CH_2\underline{C}H_3$), 1.18 (d, J = 5.9 Hz, 3H, $C_{2'}\underline{C}H_3$), 1.26 (d, J = 6.2 Hz, 3H, $C_{6'}\underline{C}H_3$), 1.29-1.35 (m, 1H, $H_{5'}$), 1.54-1.61 (m, 1H, $C_{5'}\underline{C}H_2CH_3$), 1.70-1.77 (m, 1H, $C_{5'}C\underline{H}_2CH_3$), 2.16 (d, J = 9.9 Hz, 1H, OH), 2.82 (dd, J = 13.7, 9.5 Hz, 1H, $C_4C\underline{H}_2$), 3.34 (dd, J = 13.7, 3.5 Hz, 1H, $C_4C\underline{H}_2$), 3.43 (dq, J = 10.0, 6.2 Hz, 1H, $H_{6'}$), 3.76 (dq, J = 8.9, 6.0 Hz, 1H, $H_{2'}$), 3.80-3.83 (m, 1H, $H_{3'}$), 3.84 (ddd, J = 9.8, 9.8, 9.8 Hz, 1H, H_4'), 4.16-4.23 (m, 2H, H_5), 4.68-4.72 (m, 1H, H_4), 7.25-7.27 (m, 2H, $H_{3''}$, $H_{5''}$), 7.28-7.29 (m, 1H, $H_{4''}$), 7.32-7.35 (m, 2H, $H_{2''}$, $H_{6''}$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.8 (q, $C_{5'}CH_2\underline{C}H_3$), 19.2 (t, $C_{5'}\underline{C}H_2CH_3$), 19.5 (q, $C_{6'}\underline{C}H_3$), 19.8 (q, $C_{2'}\underline{C}H_3$), 37.8 (t, $C_4\underline{C}H_2$), 50.9 (d, $C_{5'}$), 55.3 (d, $C_{3'}$), 56.1 (d, C_4), 66.3 (t, C_5), 73.6 (d, $C_{2'}$), 74.4 (d, $C_{4'}$), 75.0 (d, $C_{6'}$), 127.5 (d, $C_{4''}$), 129.1 (d, 2C, $C_{2''}$, $C_{6''}$), 129.7 (d, 2C, $C_{3''}$, $C_{5''}$), 135.3 (s, $C_{1''}$), 154.5 (s, C_2), 174.2 (s, $C_{3'}\underline{C}$(O)N); MS (EI) m/z (relative intensity): 361 $(M)^+$ (4), 344 $(M - OH)^+$ (5), 343 $(M - H_2O)^+$ (24), 228 (9), 185 (M – oxazolidin-2-one)$^+$ (13), 184 (12), 157 (M – *N*-acyl oxazolidin-2-one)$^+$ (3), 91 (100); HRMS: calcd for $C_{20}H_{27}NO_5$ $[(M)^+]$ 361.1889, found 361.1903.

(S)-3-((2R,3S,4R,5R,6S)-5-Ethyl-4-hydroxy-2,6-dimethyltetrahydro-2H-pyran-3-carbonyl)-4-isopropyloxazolidin-2-one ***(21b)***. Aldol **2k** (58 mg, 0.22 mmol) and acetaldehyde (0.1 mL of a 3.3 M solution in DCM, 0.33 mmol, 1.5 equiv) were submitted to the general procedure for the synthesis of the bicycles **5** (two-steps EAP) and yielded, after purification by flash chromatography (28 cm of height of silica gel, *n*-hexane/EtOAc 85/15), title compound **21b** (11 mg, 16%, >95:5 dr) and previously described bicycle **5ah** (29 mg, 43%, 92:8 dr). Appearance: thick colorless oil; R_F: 0.37 (*n*-hexane/EtOAc 60/40); $[\alpha]^{25}_D$ +97.9 (*c* 0.9, $CHCl_3$); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.91 (t, J = 7.6 Hz, 3H, $C\underline{H}_3CH_2C_{5'}$), 0.93 (t, J = 7.3 Hz, 6H, 2x$(C\underline{H}_3)_2CHC_3$), 1.16 (d, J = 5.8 Hz, 3H, $C\underline{H}_3C_{2'}$), 1.25 (d, J = 6.2 Hz, 3H, $C\underline{H}_3C_{6'}$), 1.26-1.30 (m, 1H, $H_{5'}$), 1.51-1.57 (m, 1H, 1x $CH_3C\underline{H}_2C_{5'}$), 1.66-1.74 (m, 1H, 1x $CH_3C\underline{H}_2C_{5'}$), 2.16 (d,

J = 10.4 Hz, 1H, OH),[85] 2.43-2.49 (m, 1H, $(CH_3)_2C\underline{H}C_3$), 3.39 (dq, J = 10.0, 6.0 Hz, 1H, $H_{6'}$), 3.72 (dq, J = 9.2, 6.1 Hz, 1H, $H_{2'}$), 3.75 (dd, J = 10.0, 9.4 Hz, 1H, $H_{4'}$), 3.82 (dd, J = 9.3, 9.3 Hz, 1H, $H_{3'}$), 4.24 (dd, J = 9.2, 2.8 Hz, 1H, H_5), 4.29 (dd, J = 9.2, 7.7 Hz, 1H, H_5), 4.46 (ddd, J = 7.9, 3.7, 2.6 Hz, 1H, H_4); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.9 (q, $\underline{C}H_3CH_2C_{5'}$), 14.8 (q, 1x$(\underline{C}H_3)_2CHC_3$), 18.1 (q, 1x$(\underline{C}H_3)_2CHC_3$), 19.3 (t, $CH_3\underline{C}H_2C_{5'}$), 19.5 (q, $\underline{C}H_3C_{6'}$), 19.8 (q, $\underline{C}H_3C_{2'}$), 28.7 (d, $(CH_3)_2\underline{C}HC_3$), 51.1 (d, $C_{5'}$), 55.1 (d, $C_{3'}$), 59.4 (d, C_4), 63.7 (t, C_5), 73.5 (d, $C_{2'}$), 74.5 (d, $C_{4'}$), 75.0 (d, $C_{6'}$), 155.2 (s, C_2), 174.0 (s, $C_{3'}C(O)N$); MS (EI) m/z (relative intensity): 297 $(M - H - Me)^+$ (1), 295 $(M - H_2O)^+$ (26), 283 $(M - Et - H)^+$ (1),[86] 271 $(M + 1 - i\text{-}Pr)^+$ (1), 228 (M + H – Et – Me – *i*-Pr)$^+$ (2),[87] 185 (M – oxazolidin-2-one)$^+$ (4), 157 (M – *N*-acyl oxazolidin-2-one)$^+$ (1),[88] 156 (*N*-acyl oxazolidin-2-one)$^+$ (5);[88] HRMS: calcd for $C_{16}H_{25}NO_4$ $[(M - H_2O)^+]$ 295.1784, found 295.1782.

*(S)-3-((2R,3S,4R,5R,6S)-5-Ethyl-4-hydroxy-6-methyl-2-phenethyltetrahydro-2H-pyran-3-carbonyl)-4-isopropyloxazolidin-2-one (**21c**)*. Aldol **2l** (43 mg, 0.12 mmol) and acetaldehyde (0.05 mL of a 3.3 M solution in DCM, 0.18 mmol, 1.5 equiv) were submitted to the general procedure for the synthesis of the bicycles **5** (two-steps EAP) and yielded, after purification by flash chromatography (28 cm of height of silica gel, *n*-hexane/EtOAc 90/10), title compound **21c** (6 mg, 12%, >95:5 dr) and previously described bicycle **5ai** (22 mg, 45%, >95:5 dr). Appearance: white solid (probably crystalline); R_F: 0.63 (*n*-hexane/EtOAc 70/30 three times); $[\alpha]^{25}_D$ +61.9 (*c* 0.3, $CHCl_3$); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.89-0.92 (m, 9H, 2x $(C\underline{H}_3)_2CH$, $C\underline{H}_3CH_2$), 1.27-1.32 (m, 1H, $H_{5'}$), 1.29 (d, J = 6.0 Hz, 3H, $CH_3C_{6'}$), 1.56-1.61 (m, 1H, $CH_3C\underline{H}_2$), 1.62-1.78 (m, 3H, $C\underline{H}_2CH_2Ph$, $CH_3C\underline{H}_2$), 2.15 (d, J = 10.7 Hz, 1H, OH), 2.40-2.48 (m, 1H, $(CH_3)_2C\underline{H}$), 2.57-2.63 (m, 1H, $CH_2C\underline{H}_2Ph$), 2.85-2.91 (m, 1H, $CH_2C\underline{H}_2Ph$), 3.36 (dq, J = 10.0, 6.0 Hz, 1H, $H_{6'}$), 3.61 (td, J = 9.5, 2.4 Hz, 1H, $H_{2'}$), 3.73 (ddd, J = 10.4, 10.4,

10.4 Hz, 1H, $H_{4'}$), 3.89 (dd, J = 9.9, 9.9 Hz, 1H, $H_{3'}$), 4.19-4.26 (m, 2H, H_5), 4.39-4.42 (m, 1H, H_4), 7.16-7.19 (m, 3H, Ph), 7.24-7.28 (m, 2H, Ph); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.9 (q, $\underline{C}H_3CH_2$), 14.8 (q, $(\underline{C}H_3)_2CH$), 18.1 (q, $(\underline{C}H_3)_2CH$), 19.3 (t, $CH_3\underline{C}H_2$), 19.5 (q, $\underline{C}H_3C_{6'}$), 28.6 (d, $(CH_3)_2\underline{C}H$), 32.1 (t, $CH_2\underline{C}H_2Ph$), 35.8 (t, $\underline{C}H_2CH_2Ph$), 51.5 (d, $C_{5'}$), 53.8 (d, $C_{3'}$), 59.4 (d, C_4), 63.6 (t, C_5), 74.9 (d, $C_{4'}$), 75.1 (d, $C_{6'}$), 76.7 (d, $C_{2'}$), 126.0 (d, Ph), 128.5 (d, 2C, Ph), 128.6 (d, 2C, Ph), 142.3 (s, Ph), 155.2 (s, C_2), 174.0 (s, $C_{3'}\underline{C}(O)N$); MS (EI) m/z (relative intensity): 403 $(M)^+$ (4), 388 $(M - Me)^+$ (6), 385 $(M - H_2O)^+$ (12), 316 $(M - H - Et - Me - i\text{-}Pr)^+$ (3), 298 $(M - CH_2CH_2Ph)^+$ (4), 275 (M – oxazolidin-2-one)$^+$ (2), 256 (M – H – H_2O – oxazolidin-2-one) (59), 248 (M + H – *N*-acyl oxazolidin-2-one)$^+$ (6),[89] 158 (*N*-acyl oxazolidin-2-one + 2)$^+$ (9),[89] 130 (oxazolidin-2-one + 2)$^+$ (74);[89] HRMS: calcd for $C_{23}H_{33}NO_5$ $[(M)^+]$ 403.2359, found 403.2353.

*(4R,5S)-3-((2S,3R,4S,5S,6R)-2,6-Dibutyl-5-ethyl-4-hydroxytetrahydro-2H-pyran-3-carbonyl)-4-methyl-5-phenyloxazolidin-2-one (**21d**)*. Aldol **2m** (22 mg, 60 mmol) was submitted to the general procedure for the synthesis of the bicycles **5** (two-steps EAP) and yielded, after purification by flash chromatography (18 cm of height of silica gel, 600 mL of *n*-hexane/EtOAc 90/10 to remove nonpolar impurities[90] and then 200 mL of EtOAc), title compound **21d** (2.7 mg, 10%, >95:5 dr) as a colorless oil. R_F: 0.69 (EtOAc); $[\alpha]^{25}_D$ –13.9 (*c* 0.3, $CHCl_3$); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.81 (t, J = 7.2 Hz, 3H, $C\underline{H}_3CH_2CH_2CH_2$), 0.85-0.94 (m, 6H, $C\underline{H}_3CH_2C_{5'}$ and $C\underline{H}_3CH_2CH_2CH_2$), 1.14-1.55 (m, 13H, $H_{5'}$, 12H from CH_2), 1.63-1.68 (m, 1H, 1H from CH_2), 1.69-1.75 (m, 1H, 1x$CH_3C\underline{H}_2C_{5'}$), 2.01 (d, J = 9.2 Hz, 1H, OH), 3.20 (td, J = 9.7, 2.1 Hz, 1H, $H_{6'}$), 3.46 (td, J = 9.4, 2.6 Hz, 1H, $H_{2'}$), 3.77-3.85 (m, 1H, $H_{4'}$), 3.85-3.88 (m, 1H, $H_{3'}$), 4.47 (qd, J = 6.3, 2.8 Hz, 1H, H_4), 5.11 (d, J = 2.5 Hz, 1H, H_5), 7.27-7.28 (m, 1H, Ph), 7.30-7.36 (m, 1H, Ph), 7.38-7.43 (m, 3H); ^{13}C-NMR (150 MHz, δ, $CDCl_3$):

9.8 (q, $\underline{C}H_3CH_2C_{5'}$), 14.1 (q, $\underline{C}H_3CH_2CH_2CH_2C_{2'}$), 14.3 (q, $\underline{C}H_3CH_2CH_2CH_2C_{2'}$), 19.0 (t, $CH_3\underline{C}H_2C_{5'}$), 19.8 (q, $\underline{C}H_3C_4$), 22.6 (t, $CH_3\underline{C}H_2CH_2CH_2C_{2'}$), 22.7 (t, $CH_3\underline{C}H_2CH_2CH_2C_{2'}$), 27.75 (t, $CH_3CH_2\underline{C}H_2CH_2C_{2'}$), 27.82 (t, $CH_3CH_2\underline{C}H_2CH_2C_{2'}$), 32.5 (t, $CH_3CH_2CH_2\underline{C}H_2C_{2'}$), 33.6 (t, $CH_3CH_2CH_2\underline{C}H_2C_{2'}$), 49.2 (d, $C_{5'}$), 54.4 (d, $C_{3'}$), 58.7 (d, C_4), 74.7 (d, $C_{4'}$), 77.4 (d, $C_{2'}$), 78.3 (d, $C_{6'}$), 81.8 (d, C_5), 125.1 (d, 2C, Ph), 129.3 (d, 2C, Ph), 129.5 (d, Ph), 137.6 (s, Ph), 154.1 (s, C_2), 174.3 (s, $C_{3'}C(O)N$); MS (EI) m/z (relative intensity): 445 $(M)^+$ (1), 428 $(M - OH)^+$ (18), 427 $(M - H_2O)^+$ (61), 388 $(M - Bu)^+$ (22), 373 $(M - Bu - Me)^+$ (2), 359 $(M - Bu - Et)^+$ (1), 339 $(M - Et - Ph)^+$ (21), 302 $(M - 2\ Bu - Et)^+$ (1), 250 $(M - Et - Bu - H_2O - Me - Ph)^+$ (100), 240 (M + 1 – *N*-acyl oxazolidin-2-one)$^+$ (3), 204 (*N*-acyl oxazolidin-2-one)$^+$ (4), 178 (oxazolidin-2-one + 2)$^+$ (49);[91] HRMS: calcd for $C_{26}H_{37}NO_4$ $[(M - H_2O)^+]$ 427.2723, found 427.2704.

ASSOCIATED CONTENT

Molecules index which correlates the numeration of the molecules discussed herein with those exposed in our previous report;[30] list of the products submitted to biological evaluation; NMR analysis of the minor diastereoisomer obtained during the synthesis of bicycle **5a**; comparison of representative signals of **1b-Br**, **5b** and **7b-Br** in NMR spectra; NMR analysis of bicycle **5e** and its minor diastereoisomers, as well as a mechanistic proposal for their obtaining; mechanistic proposal and NMR evolution of the conversion of *anti*-aldol **9a** into products **10b** and **12**; helpful information for the identification of bicycles **5** and THPs-Xc **21**; chiral HPLC chromatograms; screening of Lewis acids for the enantiomeric version of Prins cyclization; DFT calculation results; copies of ^1H and ^{13}C NMR spectra for new products and 2D NMR spectra for representative products.

ACKNOWLEDGMENTS

This research was supported by the Spanish MINECO (CTQ2011-28417-C02-01, CTQ2014-56362-C2-1-P and SAF2015-65113-C2-1-R), cofinanced by the European Regional Development Fund (ERDF), IMBRAIN project (FP7-REGPOT-2012-CT2012-31637-IMBRAIN), funded under the 7th Framework Programme (CAPACITIES). M.L.V. thanks CONICET for a post-doctoral grant. M.D.P. thanks EU Social Fund (FSE) and ACIISI for a pre-doctoral fellowship. The authors thank graduate student José Gregorio Clemente Barrera and PhD student Samuel Delgado-Hernández for their helpful assistance in the synthesis of some starting materials.

REFERENCES AND ENDNOTES

[1] Martín, T.; Padrón, J. I.; Martín, V. S. Strategies for the Synthesis of Cyclic Ethers of Marine Natural Products. *Synlett* **2014**, *25*, 12–32 and references therein.

[2] Su, B.-N.; Takaishi, Y.; Kusumi, T. Morinols A-L, Twelve Novel Sesquineolignans and Neolignans With a New Carbon Skeleton from *Morina chinensis*. *Tetrahedron* **1999**, *55*, 14571–14586.

[3] Yamauchi, S.; Kawahara, S.; Wukirsari, T.; Nishiwaki, H.; Nishi, K.; Sugahara, T.; Akiyama, K.; Kishida, T. Structure–Cytotoxic Activity Relationship of Sesquilignan, Morinol A. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4923–4930.

[4] Akiyama, K.; Yamauchi, S.; Maruyama, M.; Sugahara, T.; Kishida, T.; Koba, Y. Antimicrobial Activity of Stereoisomers of Morinols A and B, Tetrahydropyran Sesquineolignans. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 129–133.

[5] Masuda, K.; Nishiwaki, H.; Akiyama, K.; Yamauchi, S.; Maruyama, M.; Sugahara, T.; Kishida, T. Antifungal Activity of Morinol B Derivatives of Tetrahydropyran Sesquilignan. *Biosci. Biotechnol. Biochem*. **2010**, *74*, 2071–2076.

[6] (a) Erickson, K. L.; Gustafson, K. R.; Pannell, L. K.; Beutler, J. A.; Boyd, M. R. New Dimeric Macrolide Glycosides from the Marine Sponge *Myriastra clavosa*. *J. Nat. Prod.* **2002**, *65*, 1303–1306; (b) Rao, M. R.; Faulkner, D. J. Clavosolides A and B, Dimeric Macrolides from the Philippines Sponge *Myriastra clavosa*. *J. Nat. Prod.* **2002**, *65*, 386–388.

[7] For the isolation of polycavernosides A2, A3 and B2, see: (a) Yotsu-Yamashita, M.; Seki, T.; Paul, V. J.; Naoki, H.; Yasumoto, T. Four New Analogs of Polycavernoside A. *Tetrahedron Lett.* **1995**, *36*, 5563–5566; for the isolation of polycavernosides A and B, see: (b) Yotsu-Yamashita, M.; Haddock, R. L.; Yasumoto, T. Polycavernoside A: a Novel Glycosidic Macrolide from the Red Alga *Polycavernosa tsudai* (Gracilaria edulis). *J. Am. Chem. Soc.* **1993**, *115*, 1147–1148.

[8] Martin, H. J.; Magauer, T.; Mulzer, J. In Pursuit of a Competitive Target: Total Synthesis of the Antibiotic Kendomycin. *Angew. Chem. Int. Ed.* **2010**, *49*, 5614–5626 and references therein.

[9] Searle, P. A.; Molinski, T. F. Phorboxazoles A and B: Potent Cytostatic Macrolides from Marine Sponge Phorbas species. *J. Am. Chem. Soc.* **1995**, *117*, 8126–8131.

[10] Ghosh, A. K.; Anderson, D. D. Tetrahydrofuran, Tetrahydropyran, Triazoles and Related Heterocyclic Derivatives as HIV Protease Inhibitors. *Fut. Med. Chem.* **2011**, *3*, 1181–1197.

[11] (a) Capim, S. L.; Gonçalves, G. M.; dos Santos, G. C. M.; Marinho, B. G.; Vasconcellos M. L. A. A. High Analgesic and Anti-Inflammatory in vivo Activities of Six New Hybrids NSAIAs Tetrahydropyran Derivatives. *Bioorg. Med. Chem*. **2013**, *21*, 6003–6010; (b) Capim, S. L.; Carneiro, P. H. P.; Castro, P. C.; Barros, M. R. M.; Marinho, B. G.; Vasconcellos M. L. A. A. Design, Prins-Cyclization Reaction Promoting Diastereoselective Synthesis of 10 New Tetrahydropyran Derivatives and *in vivo* Antinociceptive Evaluations. *Eur. J. Med. Chem.* **2012**, *58*, 1–11.

[12] Kharkar, P. S.; Reith, M. E. A.; Dutta, A. K. Three-Dimensional Quantitative Structure-Activity Relationship (3D QSAR) and Pharmacophore Elucidation of Tetrahydropyran Derivatives as Serotonin and Norepinephrine Transporter Inhibitors. *J. Comput. Aided Mol. Des.* **2008**, *22*, 1–17.

[13] (a) Surivet, J.-P.; Zumbrunn, C.; Rueedi, G.; Bur, D.; Bruyère, T.; Locher, H.; Ritz, D.; Seiler, P.; Kohl, C.; Ertel, E. A.; Hess, P.; Gauvin, J.-C.; Mirre, A.; Kaegi, V.; dos Santos, M.; Kraemer, S.; Gaertner, M.; Delers, J.; Enderlin-Paput, M.; Weiss, M.; Sube, R.; Hadana, H.; Keck, W.; Hubschwerlen, C. Novel Tetrahydropyran-Based Bacterial Topoisomerase Inhibitors with Potent Anti-Gram Positive Activity and Improved Safety Profile. *J. Med. Chem.* **2015**, *58*, 927–942; (b) Surivet, J.-P.; Zumbrunn, C.; Bruyère, T.; Bur, D.; Kohl, C.; Locher, H. H.; Seiler, P.; Ertel, E. A.; Hess, P.; Enderlin-Paput, M.; Enderlin-Paput, S.; Gauvin, J.-C.; Mirre, A.; Hubschwerlen, C.; Ritz, D.; Rueedi, G. Synthesis and Characterization of Tetrahydropyran-Based Bacterial Topoisomerase Inhibitors with Antibacterial Activity against Gram-Negative Bacteria. *J. Med. Chem.* **2017**, *60*, 3776–3794.

[14] For the biological evaluation of THPs synthesized in our research group, see: (a) León, L. G.; Miranda, P. O.; Martín, V. S.; Padrón, J. I.; Padrón, J. M. Antiproliferative Activity of 2-Alkyl-4-Halopiperidines and 2-Alkyl-4-Halo-1,2,5,6-Tetrahydropyridines in Solid Tumor Cell Lines. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2681–2684; (b) Carrillo, R.; León, L. G.; Martín, T.; Martín, V. S.; Padrón, J. M. Synthesis and Antiproliferative Activity of (2*R*,3*R*)-Disubstituted Tetrahydropyrans. Part 2: Effect of Side Chain Homologation. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 780–783; (c) Miranda, P. O.; León, L. G.; Martín, V. S.; Padrón, J. I.; Padrón, J. M. One-pot Synthesis and SAR Study of *cis*-2,6-Dialkyl-4-Chloro-Tetrahydropyrans. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3135–3138.

[15] Muzart, J. Pd^0- and Pd^{II}-Catalyzed Oxaheterocyclization of Substrates Having Both an Allylic Leaving Group and a Hydroxylated Tether. *J. Mol. Catal. A: Chem.* **2010**, *319*, 1–29.

[16] Smith III, A. B.; Fox, R. J.; Razler, T. M. Evolution of the Petasis−Ferrier Union/Rearrangement Tactic: Construction of Architecturally Complex Natural Products Possessing the Ubiquitous *cis*-2,6-Substituted Tetrahydropyran Structural Element. *Acc. Chem. Res.* **2008**, *41*, 675–687.

[17] Larrosa, I.; Romea, P.; Urpí, F. Synthesis of Six-Membered Oxygenated Heterocycles through Carbon–Oxygen Bond-Forming Rreactions. *Tetrahedron* **2008**, *64*, 2683–2723.

[18] Boivin, T. L. B. Synthetic Routes to Tetrahydrofuran, Tetrahydropyran, and Spiroketal Units of Polyether Antibiotics and a Survey of Spiroketals of Other Natural Products. *Tetrahedron* **1987**, *43*, 3309–3362.

[19] For two recent overviews regarding the strategies employed in the building of THPs in the context of the synthesis of natural products, see: (a) Nasir, N. M.; Ermanis, K.; Clarke, P. A. Strategies for the Construction of Tetrahydropyran Rings in the Synthesis of Natural Products. *Org. Biomol. Chem.* **2014**, *12*, 3323–3335; (b) Clarke, P. A.; Santos, S. Strategies for the Formation of Tetrahydropyran Rings in the Synthesis of Natural Products. *Eur. J. Org. Chem.* **2006**, *9*, 2045–2053.

[20] For the original Prins reaction, see: (a) Prins, H. J. Condensation of Formaldehyde with Some Unsaturated Compounds. *Chem. Weekblad* **1919**, *16*, 64–74, 1072–1073, 1510–1526. For the first examples of the application of the Prins cyclization to yield THPs, see: (b) Stapp, P. R. The Reaction of α Olefins with Paraformaldehyde and Hydrogen Halides. A Novel Tetrahydropyran Synthesis. *J. Org. Chem.* **1969**, *34*, 479–485; (c) Hanschke, E. Zur Kenntnis der Prinsschen Reaktion III. Mitteil.: Über die Reaktion von Allylcarbinol mit Aldehyden und Ketonen. *Chem. Ber.* **1955**, *88*, 1053–1061.

[21] For recent reviews in Prins cyclization, see: (a) McDonald, B. R.; Scheidt, K. A. Pyranone Natural Products as Inspirations for Catalytic Reaction Discovery and Development. *Acc. Chem. Res.* **2015**, *48*, 1172–1183; (b) Greco, S. J.; Fiorot, R. G.; Lacerda, V., Jr.; dos Santos, R. B. Recent Advances in the Prins Cyclization. *Aldrichim. Acta* **2013**, *46*, 59–67; (c) Han, X.; Peh, G.; Floreancig, P. E. Prins□Type Cyclization Reactions in Natural Product Synthesis. *Eur. J. Org. Chem.* **2013**, *7*, 1193–1208; (d) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. Synthesis of Tetrahydropyrans and Related Heterocycles via Prins Cyclization; Extension to Aza-Prins Cyclization. *Tetrahedron* **2010**, *66*, 413–445; (e) Crane, E. A.; Scheidt, K. A. Prins-Type Macrocyclizations as an Efficient Ring-Closing Strategy in Natural Product Synthesis. *Angew. Chem. Int. Ed.* **2010**, *49*, 8316–8326; (f) Pastor, I. M.; Yus, M. The Prins Reaction: Advances and Applications. *Curr. Org. Chem.* **2007**, *11*, 925–957.

[22] For selected previous reports of our research group, see: (a) Scoccia, J.; Pérez, S. J.; Sinka, V.; Cruz, D. A.; López-Soria, J. M.; Fernández, I.; Martín, V. S.; Miranda, P. O.; Padrón, J. I. Direct Access to 2,3,4,6-Tetrasubstituted Tetrahydro-2*H*-pyrans via Tandem S_N2'–Prins Cyclization. *Org. Lett.* **2017**, *19*, 4834–4837; (b) Pérez, S. J.; Purino, M.; Miranda, P. O.; Martín, V. S.; Fernández, I.; Padrón, J. I. Prins Cyclization Catalyzed by a Fe^{III}/Trimethylsilyl Halide System: The Oxocarbenium Ion Pathway versus the [2+2] Cycloaddition. *Chem. Eur. J.* **2015**, *21*, 15211–15217; (c) Purino, M. A.; Ramírez, M. A.; Daranas, A. H.; Martín, V. S.; Padrón, J. I. Iron(III) Catalyzed Direct Synthesis of *cis*-2,7-Disubstituted Oxepanes. The Shortest Total Synthesis of (+)-Isolaurepan. *Org. Lett.* **2012**, *14*, 5904–5907; (d) Miranda, P. O.; Carballo, R. M.; Martín, V. S.; Padrón, J. I. A New Catalytic Prins Cyclization Leading to Oxa- and Azacycles. *Org. Lett.* **2009**, *11*, 357–360; (e) Miranda, P. O.; Ramírez, M. A.; Martín, V. S.; Padrón,

J. I. The Silylalkyne-Prins Cyclization: Stereoselective Synthesis of Tetra- and Pentasubstituted Halodihydropyrans. *Org. Lett.* **2006**, *8*, 1633–1636.
[23] Tay, G. C.; Huang, C. Y.; Rychnovsky, S. D. Silyl Enol Ether Prins Cyclization: Diastereoselective Formation of Substituted Tetrahydropyran-4-ones. *J. Org. Chem.* **2014**, *79*, 8733–8749.
[24] Zheng, K.; Liu, X.; Qin, S.; Xie, M.; Lin, L.; Hu, C.; Feng, X. Completely OH-Selective $FeCl_3$-Catalyzed Prins Cyclization: Highly Stereoselective Synthesis of 4-OH-Tetrahydropyrans. *J. Am. Chem. Soc.* **2012**, *134*, 17564–17573.
[25] Elliot, M. C.; El Sayed, N. N. E.; Paine, J. S. Diastereospecific Tandem Prins Cyclisation/Rearrangement Reactions for the Desymmetrisation of Cyclohexa□1,4□dienes. *Eur. J. Org. Chem.* **2007**, *5*, 792–803.
[26] Yang, X. F.; Mague, J. T.; Li, C. J. Diastereoselective Synthesis of Polysubstituted Tetrahydropyrans and Thiacyclohexanes via Indium Trichloride Mediated Cyclizations. *J. Org. Chem.* **2001**, *66*, 739–747.
[27] Bahnck, K. B.; Rychnovsky, S. D. Formal Synthesis of (−)-Kendomycin Featuring a Prins-Cyclization To Construct the Macrocycle. *J. Am. Chem. Soc.* **2008**, *130*, 13177–13181.
[28] Bahnck, K. B.; Rychnovsky, S. D. Rapid Stereocontrolled Assembly of the Fully Substituted C-Aryl Glycoside of Kendomycin with a Prins Cyclization: a Formal Synthesis. *Chem. Commun.* **2006**, *22*, 2388–2390.
[29] Rychnovsky, S. D.; Thomas, C. R. Synthesis of the C22−C26 Tetrahydropyran Segment of Phorboxazole by a Stereoselective Prins Cyclization. *Org. Lett.* **2000**, *2*, 1217–1219.
[30] Álvarez-Méndez, S. J.; García, C.; Martín, V. S. The Evans Aldol–Prins Cyclization: a General and Stereoselective Method for the Synthesis of 2,3,4,5,6-Pentasubstituted Tetrahydropyrans. *Chem. Commun.* **2016**, *52*, 3380–3383.
[31] As drawn herein, aldols **2** show their *N*-acyl oxazolidin-2-one and R^2 groups in a *trans* orientation, which correspond to a *syn* relative stereochemistry due to the *syn*/*anti* nomenclature is established with the molecule in a zigzag projection.
[32] Evans, D. A.; Bartroli, J.; Shih, T. L. Enantioselective Aldol Condensations. 2. Erythro-Selective Chiral Aldol Condensations via Boron Enolates. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
[33] Morita, A.; Kuwahara, S. Enantioselective Total Synthesis of Litseaverticillols A and B. *Org. Lett.* **2006**, *8*, 1613–1616.
[34] Zhang, S.-J.; Hu, W.-X. Method for Regio- and Stereoselective Synthesis of (*E*)-β,γ-Unsaturated Acids from Aldehydes Under Solvent-Free Conditions. *Synth. Commun.* **2010**, *40*, 3093–3100.
[35] Rodeschini, V.; Boiteau, J.-G.; Van de Weghe, P.; Tarnus, C.; Eustache, J. MetAP-2 Inhibitors Based on the Fumagillin Structure. Side-Chain Modification and Ring-Substituted Analogues. *J. Org. Chem.* **2004**, *69*, 357–373.
[36] Andrade, C. K. Z.; Rocha, R. O.; Vercillo, O. E.; Silva, W. A.; Matos, R. A. F. DCC/DMAP-Mediated Coupling of Carboxylic Acids with Oxazolidinones and Thiazolidinethiones. *Synlett* **2003**, *15*, 2351–2352.
[37] It is described that compound *E*-α,β-**3b** reacts in an aldol addition providing the same β,γ-unsaturated alcohol **2** expected to be obtained from desired β,γ-**3b**. Thus, this mixture is not a problem since a synthetic point of view to achieve our goals. For a previously reported example, see: Nakamura, T.; Oshida, M.; Nomura, T.; Nakazaki, A.; Kobayashi, S. Synthetic Study of Diversifolin: The Construction of 11-Oxabicyclo[6.2.1]undec-3-ene Core Using Ring-Closing Metathesis. *Org. Lett.* **2007**, *9*, 5533–5536, Supporting Information page S4.
[38] Raimundo, B. C.; Heathcock, C. H. Further Studies on the Anti-Selective Aldol Reaction of Chiral Imides. *Synlett* **1995**, *12*, 1213–1214.
[39] Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. Diastereoselective Magnesium Halide-Catalyzed *anti*-Aldol Reactions of Chiral *N*-Acyloxazolidinones. *J. Am. Chem. Soc.* **2002**, *124*, 392–393.
[40] May, A. E.; Connell, N. T.; Dahlmann, H. A.; Hoye, T. R. A Useful Modification of the Evans Magnesium Halide Catalyzed *anti*-Aldol Reaction: Application to Enolizable Aldehydes. *Synlett* **2010**, *13*, 1984–1986.
[41] See Supporting Information for the mechanism of the 2-oxonia-Cope rearrangement (Schemes S2 and S3, as part of other peripheral discussions). For a detailed mechanism of both Prins cyclization and the competitive processes, see: Kataoka, K.; Ode, Y.; Matsumoto, M.; Nokami, J. Convenient Synthesis of Highly Optically Active 2,3,4,6-Tetrasubstituted Tetrahydropyrans via Prins Cyclization Reaction (PCR) of Optically Active Homoallylic Alcohols with Aldehydes. *Tetrahedron* **2006**, *62*, 2471–2483.
[42] Barry, C. St. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. Stereoselective Synthesis of 4-Hydroxy-2,3,6-trisubstituted Tetrahydropyrans. *Org. Lett.* **2003**, *5*, 2429–2432.

[43] Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T. L.; Shaka, A. J. Excitation Sculpting in High-Resolution Nuclear Magnetic Resonance Spectroscopy: Application to Selective NOE Experiments. *J. Am. Chem. Soc.* **1995**, *117*, 4199–4200.
[44] Feuillet, F. J. P.; Niyadurupola, G.; Green, R.; Cheeseman, M.; Bull, S. D. Stereoselective Rearrangement of β-Hydroxy-*N*-acyloxazolidin-2-ones to Afford *N*-2-Hydroxyethyl-1,3-oxazinane-2,4-diones. *Synlett* **2005**, *7*, 1090–1094 and references therein.
[45] Thomson, C. D.; Miller, T. A.; Barthen, M. T.; Dieckhaus, C. M.; Sofia, R. D.; Macdonald, T. L. The Synthesis, in vitro Reactivity, and Evidence for Formation in Humans of 5-Phenyl-1,3-oxazinane-2,4-dione, a Metabolite of Felbamate. *Drug Metab. Dispos.* **2000**, *28*, 434–439.
[46] Kahns, A. H.; Møss, J.; Bundgaard, H. Improved Oral Bioavailability of Salicylamide in Rabbits by a 1,3-Benzoxazine-2,4-dione Prodrug. *Int. J. Pharm.* **1992**, *78*, 199–202.
[47] Sub- and supra-stoichiometric amounts of FeF_3, $RuCl_3$, $CeCl_3$, CuI, $Pd(OAc)_3$, $[Rh(OAc)_2]_2 \cdot 2H_2O$, $TiCl_4$, $Cu(OTf)_2$, $ZnCl_2$, TFA and CSA were unsuccessfully tested to perform the Prins cyclization. In all cases, except when $TiCl_4$ was employed, the starting material was recovered.
[48] See Supporting Information for a comparison of their NMR spectra highlighting their characteristic signals.
[49] Guérinot, A.; Reymond, S.; Cossy, J. Ritter Reaction: Recent Catalytic Developments. *Eur. J. Org. Chem.* **2012**, *1*, 19–28.
[50] Hu, Y.; Skalitzky, D. J.; Rychnovsky, S. D. Prins Cyclization of 4-Allyl-1,3-dioxanes Prepared from 1,3-Diol Synthons. A Rapid Entry into Functionalized Tetrahydropyrans. *Tetrahedron Lett.* **1996**, *37*, 8679–8682.
[51] Other practical aspects of the reaction were evaluated. It was compatible with a non-inert atmosphere and it showed robustness against the moisture: from aldol **2b** and acetaldehyde, **5b** was obtained as a sole product in 78% yield in the presence of 1 equiv of H_2O; when 10 equiv of H_2O were added, **5b** (60%) was obtained together with rearranged alcohol **6b** (12%). The thorough monitoring revealed that the reaction time was lower than 1 minute, although a reaction time of 30 min was customarily selected. Starting from aldol **2a** and isovaleraldehyde, no reaction was observed at –78 ºC; when that reaction was performed at –18 ºC or 0 ºC, **5a** was successfully obtained (75%, >95:5 dr): these temperatures are recommended in those cases where a worse diastereoselectivity is achieved at rt.
[52] Kishi, Y.; Inagi, S.; Fuchigami, T. Prins Cyclization in Ionic Liquid Hydrogen Fluoride Salts: Facile and Highly Efficient Synthesis of 4□Fluorinated Tetrahydropyrans, Thiacyclohexanes, and Piperidines. *Eur. J. Org. Chem*. **2009**, *1*, 103–109.
[53] By-products probably obtained due to an isomerization of *anti*-**2a** or some of its intermediates in the reaction medium. See Supporting Information for a mechanistic proposal and a detailed analysis of the NMR spectra.
[54] Kocsis, L. S.; Benedetti E.; Brummond, K. M. A Thermal Dehydrogenative Diels–Alder Reaction of Styrenes for the Concise Synthesis of Functionalized Naphthalenes. *Org. Lett.* **2012**, *14*, 4430–4433.
[55] Poulter, D. C.; Winstein, S. J. Solvolysis and Degenerate Cyclopropylcarbinyl-Cyclopropylcarbinyl Rearrangement of a Hexamethylcyclopropylcarbinyl System. *J. Am. Chem. Soc.* **1969**, *91*, 3650–3652.
[56] Reddy, B. V. S.; Yarlagadda, S.; Reddy, C. R.; Reddy, M. R.; Sridhar, B.; Satyanarayana, D.; Jagadeesh, B. Tandem Prins Strategy for the Synthesis of Spiropyrrolidine and Spiropiperidine Derivatives. *Eur. J. Org. Chem.* **2015**, *14*, 3076–3085.
[57] Xie, Y.; Cheng, G.-J.; Lee, S.; Kaib, P. S. J.; Thiel, W.; List, B. Catalytic Asymmetric Vinylogous Prins Cyclization: A Highly Diastereo- and Enantioselective Entry to Tetrahydrofurans. *J. Am. Chem. Soc.* **2016**, *138*, 14538–14541.
[58] We speculate that $BF_3 \cdot OEt_2$ forms a chelate with both the oxocarbenium ion and the MeO group, leading to a six member ring in the transition state that might alter the evolution of the cyclization to the bicyclic products.
[59] (a) Hinkle, R. J.; Chen, Y.; Nofi, C. P.; Lewis, S. E. Electronic Effects on a One-pot Aromatization Cascade Involving Alkynyl-Prins Cyclization, Friedel–Crafts Alkylation and Dehydration to Tricyclic Benzo[*f*]isochromenes. *Org. Biomol. Chem.* **2017**, *15*, 7584-7593; (b) Barry, C. S.; Bushby, N.; Harding, J. R.; Hughes, R. A.; Parker, G. D.; Roe, R.; Willis, C. L. Probing the Mechanism of Prins Cyclisations and Application to the Synthesis of 4-Hydroxytetrahydropyrans. *Chem. Commun.* **2005**, *29*, 3727–3729.
[60] Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. Utilization of an Oxonia-Cope Rearrangement as a Mechanistic Probe for Prins Cyclizations. *J. Am. Chem. Soc.* **2005**, *127*, 9939–9945.
[61] Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. Oxonia-Cope Rearrangement and Side-Chain Exchange in the Prins Cyclization. *Org. Lett.* **2002**, *4*, 577–580.
[62] During the synthesis of **5w** we unsuccessfully tried to avoid the undesired obtaining of **6c** by repeating the reaction at different concentration (1 M and 0.01 M) and temperatures (–78 ºC), but a similar

proportion was always obtained. Gratifying, we finally were able to improve the low yield by changing DCM to *n*-hexanes as solvent (50% of **5w** and 30% of **6c**). As product **6c** is a homoallylic alcohol susceptible to suffer a Prins cyclization, we tested its reactivity as an alternative precursor of the bicycle **5w**. It was submitted to the standard conditions (2.5 equiv of $BF_3 \cdot OEt_2$, DCM 0.1 M and rt) with MeCHO (1.5 equiv) and we observed that it reacted barely to yield **5w** (24 h, 40%), bringing to light that the electronic and steric environment of the olefin in homoallylic alcohols **2** is key for the successful EAP cyclization.

[63] See Supporting Information for the NMR spectra regarding the evolution of the reaction over the time and for a mechanistic proposal.

[64] Feuillet, F. J. P.; Robinson, D. E. J. E.; Bull, S. D. An (*E*)-selective synthesis of trisubstituted (*E*)-α,β-unsaturated acid derivatives. *Chem. Commun.* **2003**, *17*, 2184–2185.

[65] Papillon, J. P. N.; Taylor, R. J. K. The Preparation of Nonracemic Secondary α-(Carbamoyloxy)alkylzinc and Copper Reagents. A Versatile Approach to Enantioenriched Alcohols. *Org. Lett.* **2002**, *4*, 119–122.

[66] Kende, A. S.; Kawamura, K.; DeVita, R. J. Enantioselective Total Synthesis of Neooxazolomycin. *J. Am. Chem. Soc.* **1990**, *112*, 4070–4072.

[67] Lange, H.; Huenerbein, R.; Wibbeling, B.; Fröhlich, R.; Grimme, S.; Hoppe, D. Comprehensive Experimental and Theoretical Studies of Configurationally Labile Epimeric Diamine Complexes of α-Lithiated Benzyl Carbamates. *Synthesis* **2008**, *18*, 2905–2918.

[68] Fuwa, H.; Saito, A.; Naito, S.; Konoki, K.; Yotsu-Yamashita, M.; Sasaki, M. Total Synthesis and Biological Evaluation of (+)□Neopeltolide and Its Analogues. *Chem. Eur. J.* **2009**, *15*, 12807–12818.

[69] D'yakonov, V. A.; Tuktarova, R. A.; Islamov, I. I.; Khalilov, L. M.; Dzhemilev, U. M. Catalytic Cyclometallation in Steroid Chemistry IV: Efficient Method for the Synthesis of Tetrahydrothiophene, Tetrahydroselenophen and Cyclopentanone Derivatives of (5α)-Cholestane. *Steroids* **2016**, *108*, 77–84.

[70] See Supporting Information for chiral HPLC of representative compound.

[71] Thorough analyses of 2D NMR, together with reproducible patterns found in the mass spectra, allowed us the unambiguous differentiation of structures **5** and **21**. GOESY analyses confirmed that both structures bear all their substituents in equatorial positions, analogously to when non-chiral substrates were used. See Supporting Information for extra details.

[72] See Supporting Information for the screening of Lewis acids for the enantiomeric version of Prins cyclization.

[73] See Supporting Information for the complete list of products evaluated.

[74] De León, L; Moujir, L. Activity and Mechanism of the Action of Zeylasterone against *Bacillus subtilis*. *J. Appl. Microbiol.* **2008**, *104*, 1266–1274.

[75] It can be even used an aldehyde freshly obtained through a Parikh-Doering oxidation, or a PCC-mediated oxidation, without further purification. Longer reaction time could lead to a bigger amount of the undesired α,β-isomer. These reactions were monitored by TLC analysis, or by ^{1}H NMR analysis of aliquots taken of the reaction medium and then treated with a few drops of a 2 M aqueous solution of H_2SO_4 and a few drops of AcOEt.

[76] A non-aqueous simplified work-up is also valid: a small amount of silica gel 60 (35-70 mesh) was added, the solvent was removed in the rotavap and the silica-supported crude was purified.

[77] When the NMR spectra were recorded using $CDCl_3$ as solvent, N<u>C</u>H(CH_2Ph)CH_2OH appeared as a weak br s in the ^{13}C spectrum, but that signal did not appear neither in DEPTs spectra nor in HSQCed. Fortunately, its correlation appeared weakly in HMBC.

[78] When $CDCl_3$ was employed as solvent, C_{8a} did not appear in DEPTs and it was difficult to study the HSQCed due to H_{8a} appeared as a br s. Fortunately, HMBC showed a clear correlation with H_{4a} y H_8.

[79] When the ^{13}C spectrum was recorded at T = 320 K and using C_6D_6 as solvent, N<u>C</u>H(CH_2Ph)CH_2OH appeared as a weak br s, although its correlations were clear in HSQCed and HMBC.

[80] In the ^{13}C spectrum, this signal appears as a br s, like in other similar bicycles. However, in this product the signal appears clearly in the DEPT90 spectrum, as well as in the HSQCed (weak correlation with H with δ = 4.34-4.40 ppm) and the HMBC (correlation with $(CH_3)_2$C<u>H</u>).

[81] This is a typical fragmentation of the bicycle and does not appear, or its intensity is lower, in the mass spectrum of the isomer **21b**.

[82] When $CDCl_3$ was employed as solvent, N<u>C</u>H(*i*-Pr)CH_2OH was not detected in C, DEPTs, HSQCed or HMBC. According to similar compounds, it should appear between 50-60 ppm.

[83] This is a typical fragmentation of the bicycle and does not appear, or its intensity is lower, in the mass spectrum of the isomer **21c**.

[84] By contrast, when a solution of bicycle **5a** in Et_2O (0.12 M) was added to an ice-cooled suspension of $LiAlH_4$ (9 equiv) in Et_2O (0.3 M) and the mixture was allowed to warm to rt, after 5 h carbamate **20** was obtained with a poor 5% yield together with traces of diol **19**.

[85] This signal shows correlation with $H_{4'}$ in COSY spectrum and with $C_{3'}$ and $C_{4'}$ in HMBC spectrum. However, these correlations do not appear in its isomer, the bicycle **5ah**.

[86] In the mass spectrum of the bicycle **5ah**, this peak may correspond to this same fragmentation but also to the typical fragmentation of a bicycle $(M + 1 - CH_2OH)^+$, which explain the higher intensity observed there (66 against 1).

[87] In the mass spectrum of the bicycle **5ah**, this peak may correspond to this same fragmentation but also to the typical fragmentation of a bicycle $(M + 2 - CH(i\text{-}Pr)CH_2OH)^+$, which explain the higher intensity observed there (94 against 2).

[88] In the mass spectrum of the bicycle **5ah**, this fragmentation does not appear due to the oxazolidin-2-one is part of the bicycle and is not prone to be removed.

[89] In the mass spectrum of the bicycle **5ai**, these fragmentations do not appear due to the oxazolidin-2-one is part of the bicycle and is not prone to be removed.

[90] No products were identified in the nonpolar fractions.

[91] In addition to the typical signals due to the fragmentation of the oxazolidin-2-one of the product, no signal with m/z 310 was detected (it would have corresponded to the fragmentation M – CH(Me)CH(Ph)OH of the bicyclic isomer).